



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 63

Alan R. Katritzky

Advances in

# Heterocyclic Chemistry

Volume 63

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Advances in

# HETEROCYCLIC CHEMISTRY

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## Preface

Volume 63 of *Advances in Heterocyclic Chemistry* comprises five chapters, from five different countries. In Chapter 1, I. D. Sadekov and V. I. Minkin (Rostov, Russia) have provided the first comprehensive survey since 1984 of six-membered heterocycles containing a tellurium atom. These compounds, which show many differences to their sulfur and selenium analogs, are of potential importance for materials applications.

The first available review of annelated 1,5-benzothiazepines, a diverse group of increasingly important polycycles, is provided by A. Chimirri and her colleagues (Messina, Italy) in Chapter 2. Recent developments in the chemistry of pyrido[1,2-*a*]pyrimidines are covered in Chapter 3 by I. Hermecz (Budapest, Hungary), an area which has more than doubled in the 12 years since his last overview in Volume 33 of these *Advances*.

The chemistry of heterocyclic hydrazonoyl halides is reviewed in Chapter 4 by A. S. Shawali and M. A. Abdallah (Cairo, Egypt). These compounds have predominantly been used as intermediates in the synthesis of heterocycles and have not previously been surveyed. Finally, J. Sepúlveda-Arques, B. Abarca-González, and M. Medio-Simón (Valencia, Spain) contributed the last chapter, "Cycloaddition Reactions with Vinyl Heterocycles" which centers on their Diels–Alder and competing reactions.

Readers are reminded that the last "index volume" of the series was Volume 60.

A. R. KATRITZKY  
Gainesville, Florida

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## Six-Membered Heterocycles with a Tellurium Atom

IGOR D. SADEKOV AND VLADIMIR I. MINKIN

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## I. Introduction

The chemistry of six-membered tellurium-containing heterocycles dates back to 1920 when Morgan successfully prepared 1-telluracyclohexane-3,5-dione (20JCS1456). In the next five years he synthesized a wide variety of derivatives of this heterocycle, completing his work in 1928 with the preparation of 1-telluracyclohexane (28JCS321). Further development of the chemistry of six-membered tellurium heterocycles was rather uneven. Until 1974, the only additional compounds of this type that were synthesized were telluraisochromane [43N(L)749] and telluraflavone (71BSB669). All the other structural types described in the present review paper have become known in the last 15–20 years. The general aspects of the synthesis and reactions of six-membered tellurium-containing heterocycles have been previously covered in the chapters of monographs (74MI1; 86MI1). The development of this branch of heterocyclic chemistry until 1984 was considered in detail in an earlier review (85MI1). Another concise review deals with the specific topic of chalcogenaxanthylum cations (83KGS435). Since then, a considerable body of new data on the preparation and reactions of six-membered tellurium-containing heterocycles has appeared in the literature, in particular, those related to heteroaromatic tellurium-containing cations. The intention of this review is to bring all of the relevant information together. To put the problem into common perspective, earlier references are included, whereas emphasis is given to the latest development of the area.

Organotellurium compounds display certain characteristic peculiarities of structure and reactivity in comparison with their sulfur and selenium analogs (90MI1). These peculiarities are caused by low C—Te bond-energy values in various types of compounds, the tendency of dicoordinate tellurium compounds to undergo oxidative addition reactions, enhanced halogenophilicity of the  $\text{RTe}^-$  anions, high electrophilicity of the  $\text{TeX}_3$  ( $\text{X} = \text{Hal}$ ) groups, and thermodynamic stability of derivatives of tetra-coordinate tellurium ( $\sigma$ -telluranes  $\text{R}^1\text{R}^2\text{TeX}_2$  and  $\text{RTeX}_3$ ). Such distinctive properties of organotellurium compounds often result in marked differences in the methods for the preparation of tellurium-containing heterocycles in comparison with their sulfur and selenium analogs. A number of standard procedures developed for the synthesis of the latter fail to afford tellurium-containing heterocycles when based on similar organotellurium precursors. At the same time the distinctive features of organotellurium compounds make it possible to employ for the preparation of tellurium-containing heterocycles reactions that are uncommon to the chemistry of organosulfur and organoselenium compounds. For the same reasons the

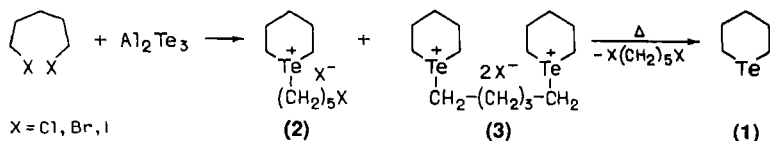
chemical behavior of tellurium-containing heterocycles is often in sharp contrast with that of their sulfur and selenium analogs.

## II. Monocyclic, Bicyclic, and Tricyclic Tellurium-Containing Heterocycles with Tellurium Atoms in Position 1

### A. 1-TELLURACYCLOHEXANE AND ITS DERIVATIVES

#### 1. Synthesis

Two different methods were employed for the synthesis of 1-telluracyclohexane **1**. The first one is based on the alkylation of aluminum (28JCS321) or sodium (45JCS11; 67JA5921) tellurides with 1,5-dihalogenopentanes. The direct products of the reaction with  $\text{Al}_2\text{Te}_3$  are telluronium salts **2** and **3**, which, like most of the compounds of this type (74MI1; 83MI2), readily eliminate alkyl halogenides to afford **1** in moderate yield.

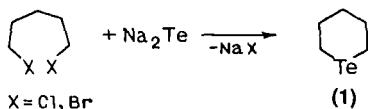


When 1,5-dibromopentane was used, a small amount of 1,1-dibromo-1-telluracyclohexane was also formed as a by-product through, most probably, partial hydrolysis of  $\text{Al}_2\text{Te}_3$  and the subsequent reaction of tellurium (from  $\text{H}_2\text{Te}$ ) with 1,5-dibromopentane.

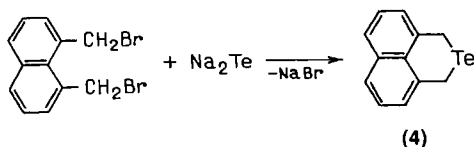
The conditions at which the reaction occurs depend on the nature of the halogen in the 1,5-dihalogenopentanes. With 1,5-diiodopentane, the reaction occurs readily when the mixture of components is heated at 135–145°C, whereas heating at substantially higher temperatures is required in the cases of 1,5-dibromo- (165°C) and 1,5-dichloropentanes (175–185°C).

Alkylation of sodium telluride with 1,5-dibromo- and 1,5-dichloropentanes serves as the most convenient one-step method of preparation of **1** (45JCS11). The yields of the reaction are 35–60%.

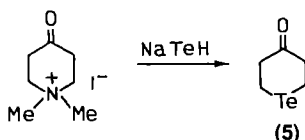
The reaction was employed for the synthesis of the deuterated deriva-



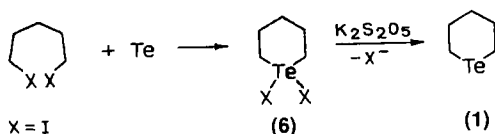
tives of **1**, namely 4,4-d<sub>2</sub>- and 3,3,5,5-d<sub>4</sub>-1-telluracyclohexane (67JA5921) and 3,5-naphtho-1-telluracyclohexane **4** (82CC333).



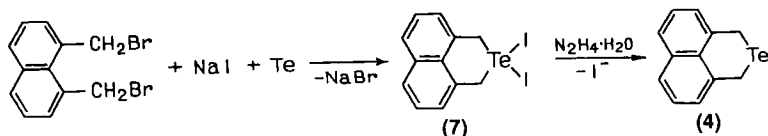
Rather scant information is available about functionalized 1-telluracyclohexanes. The only known compound of this type, 1-telluracyclohexan-4-one **5** has been obtained in 38% yield by recyclization of 1,1-dimethyl-4-piperidinonium iodide by treatment with NaTeH (85TL5441).



The second approach to the preparation of 1-telluracyclohexane involves the reaction of 1,5-diiodopentane with elemental tellurium under heating (45JCS11). Initially formed (in 63% yield) 1,1-diiodo-1-telluracyclohexane **6** (X = I) is readily reduced to **1** by potassium metabisulfite in almost quantitative yield.



The reaction has been extended to  $\alpha,\alpha$ -dichloro-*o*-xylene [78JOM(146)245] and 2,3-bis(bromomethyl)quinoxaline [84JCS(D)23]. In both cases the addition of NaI was found to facilitate the cyclization reaction. With 1,8-bis(bromomethyl)naphthalene, 1,1-diiodo-3,5-naphtho-1-telluracyclohexane **7** has been obtained by the reaction with Te and NaI in 2-methoxyethanol [88JOM(338)1].



It is worth noting that 1-telluracyclohexane **1** was also isolated as a product of the reaction of 1,5-dichloropentane with RTeLi (R = Me, Ph)

(88MI1). Other compounds formed in this reaction are  $R_2Te$ ,  $RTe(CH_2)_5Cl$ , and  $RTe(CH_2)_5TeR$ . The mechanism for this formation of **1** has not yet been elucidated.

## 2. Reactions

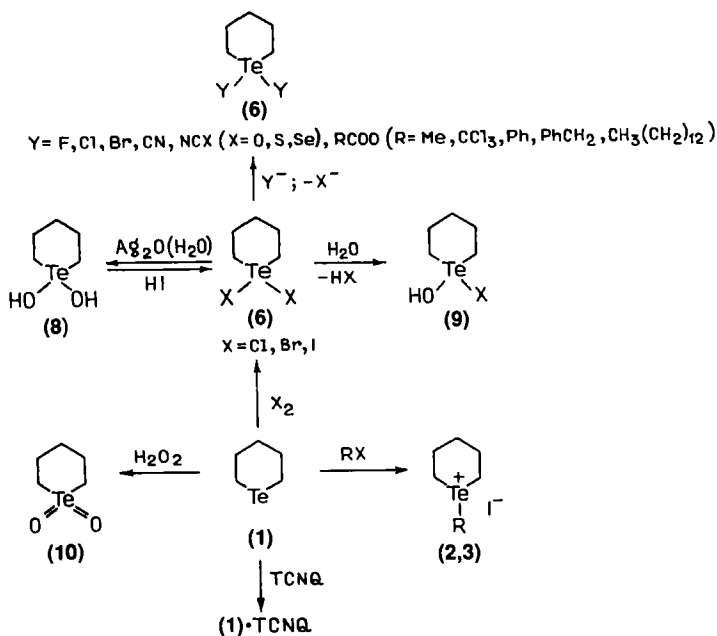
As a cyclic dialkyltelluride, 1-telluracyclohexane exhibits all the properties typical of the compounds of this class. The most characteristic is its tendency to undergo oxidative addition reactions resulting in an increase in the coordination number of the tellurium center to 3 or 4. It can be readily oxidized by chlorine, bromine, or iodine to form 1,1-dihalogeno-1-telluracyclohexanes **6** (28JCS321), which are reduced under mild conditions back to the initial heterocycle **1**. Because  $\sigma$ -telluranes **6** are stable crystalline compounds easily purified by repeated crystallization, they are often used to obtain **1** free of impurities (45JCS11).

Through exchange reactions of 1,1-diiodo-1-telluracyclohexane **6** ( $X = I$ ) with silver or potassium salts of various acids, a variety of the  $\sigma$ -telluranes **6** with electronegative substituents  $X$  attached to tellurium have been prepared in high yields [79IJC(A)71]. Hydrolysis of compounds **6** gives rise to hydroxyhalogenides **9**, whereas 1,1-dibromo-1-telluracyclohexane **6** ( $X = Br$ ) reacts with moist silver oxide to afford 1,1-dihydroxy-1-telluracyclohexane **8**. As a dialkyltellurides (74MI1; 83MI2), 1-telluracyclohexane readily forms salts of telluronium cations upon treatment with alkyl halogenides, e.g., **2** and **3** with 1,5-dihalogenopentanes (28JCS321, 28JCS2658).

Morgan (28JCS321) reported on the formation of an amorphous colorless compound insoluble in organic solvents upon oxidation of 1-telluracyclohexane by hydrogen peroxide in methanol. The compound exploded under fast heating and displayed strong oxidative properties, converting  $HCl$  to  $Cl_2$  and discoloring an aqueous solution of  $KMnO_4$ . Such chemical behavior led to the conclusion that the structure of the compound is 1-telluracyclohexane-1,1-dioxide **10**.

When allowed to react with TCNQ (tetracyanoquinodimethane), 1-telluracyclohexane **1** and its naphtho derivative **4** form stable 1 : 1 charge-transfer complexes [88JOM(338)1]. These possess long-wavelength absorption bands in the spectral region of 623–655 nm, whereas the components of the complexes do not absorb visible light. Substantial radical character of the charge-transfer complexes is corroborated by observation in their IR spectra of the  $\nu_{C\equiv N}$  vibration bands at frequencies of 2160–2205  $cm^{-1}$  characteristic of the radical-anion  $TCNQ^{\cdot-}$ . Scheme 1 summarizes the important reactions of 1-telluracyclohexane.



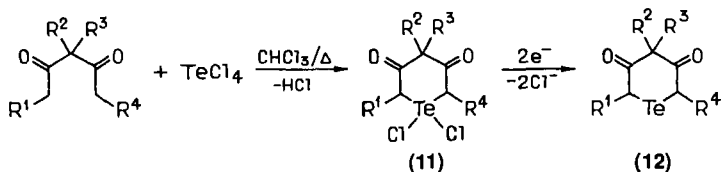


SCHEME 1

### 3. Synthesis and Reactions of 1-Telluracyclohexane-3,5-diones

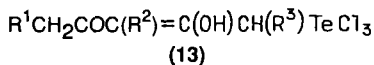
1-Telluracyclohexane-3,5-dione 1,1-dichlorides of the general type **11** are among the most thoroughly studied derivatives of 1-telluracyclohexane. These were prepared by coupling 1,3-diketones with tellurium tetrachloride in solutions of chloroform or benzene free of moisture (20JCS1456; 21JCS610; 22JCS922; 23JCS444; 24JCS731, 24JCS754, 24JCS760, 24JCS1601; 25JCS797, 25JCS2611). When treated with an aqueous solution of  $\text{K}_2\text{S}_2\text{O}_5$  or  $\text{NaHSO}_3$ , the dichlorides **11** are smoothly reduced to 1-telluracyclohexane-3,5-diones **12**. Numerous IR (64JCS688),  $^1\text{H}$  NMR (64JCS688; 76MI1) and  $^{13}\text{C}$  NMR (76JA3778, 76JA3783, 76MI1), and X-ray diffraction studies (see Section II,A,4) lent support to the validity of structure **12**, which was initially deduced from their chemical behavior of these compounds.

The structure of the organic precursors of **11** imposes certain limitations on the occurrence of the cyclization reaction, which cannot be realized unless the substituents  $\text{R}^1\text{--R}^4$  are alkyl or aralkyl (benzyl) groups or a hydrogen atom. At least one hydrogen atom must reside at a terminal

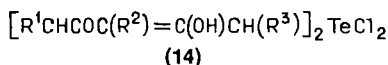


$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$ ;  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{Me, Et, Pr, Bu, C}_5\text{H}_{11}, \text{C}_6\text{H}_{13}, \text{C}_7\text{H}_{15}, \text{C}_8\text{H}_{17}, \text{C}_{10}\text{H}_{21}, \text{PhCH}_2$ ;  $\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$ ;  $\text{R}^3 = \text{Me, Et, Pr, i-Pr, Bu, i-Bu, s-Bu, PhCH}_2, \text{Cl}$ ;  
 $\text{R}^1 = \text{R}^4 = \text{H}$ ;  $\text{R}^2 = \text{R}^3 = \text{Me, Et, PhCH}_2$ ;  $\text{R}^3 = \text{R}^4 = \text{H}$ ;  $\text{R}^1 = \text{R}^2 = \text{Me, Et}$ ;  $\text{R}^3 = \text{R}^4 = \text{H}$ ;  
 $\text{R}^1 = \text{Me}$ ;  $\text{R}^2 = \text{Et, Pr, i-Pr, Bu, PhCH}_2$ ;  $\text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^1 = \text{R}^4 = \text{Me, Et}$ ,  $\text{R}^1 = \text{Me, R}^2 = \text{Et}$ ;  
 $\text{R}^1 = \text{R}^4 = \text{Me}$ ;  $\text{R}^2 = \text{H}$ ;  $\text{R}^3 = \text{Me, Et}$

carbon center, whereas the following conditions must be met for the substituents at the C(2) center:  $\text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Alk}$ ;  $\text{R}^2 = \text{Alk}$ ,  $\text{R}^3 = \text{Alk}'$ . With more electronegative phenyl or two *p*-nitrobenzyl groups attached to the C(2) atom of the initial 1,3-diketone, no cyclization reaction leading to heterocycle **11** occurs. In some cases, the reaction ceases with the formation of noncyclic organytellurium trichlorides **13** or diorganytellurium dichlorides **14**.



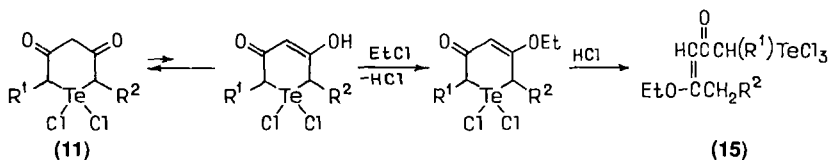
$\text{R}^1 = \text{C}_6\text{H}_{13}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^1 = \text{R}^3 = \text{Pr}$ ,  $\text{R}^2 = \text{H}$ ;  $\text{R}^1 = \text{R}^3 = \text{i-Pr}$ ,  $\text{R}^2 = \text{H}$ ;  $\text{R}^1 = \text{C}_8\text{H}_{17}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$



$\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^1 = \text{i-Pr}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Cl}$ ,  $\text{R}^3 = \text{H}$

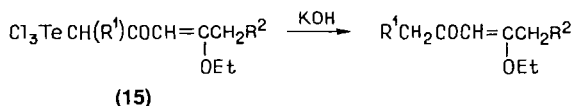
Compounds **13** and **14** are also formed in small amounts in the reactions of tellurium tetrachloride with those 1,3-diketones that afford **11** as the main product. Another by-product of the reaction, when it proceeds in chloroform admixed with ethanol, is the tellurium trichloride **15**. A conceivable mechanism for its formation is given by the following sequence of reactions.

It is likely that ethyl chloride, formed as an intermediate upon the interaction of ethanol with HCl (the latter originates from coupling 1,3-diketones with  $\text{TeCl}_4$ ), plays an important role. This conclusion is con-

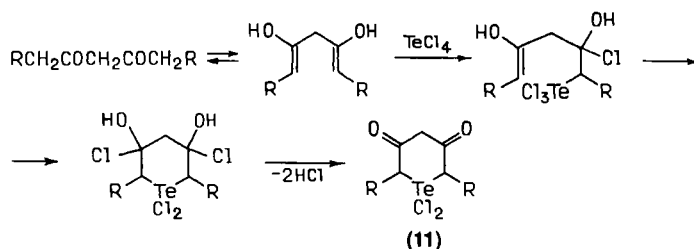


firmed by the fact that tellurium trichlorides **15** are obtained in high yields in the reaction of **11** with ethyl chloride in the presence of HCl.

When heated with KOH, compounds **15** decompose to give 3-ethoxypropenones, thereby allowing one to consider this reaction a specific route for *O*-alkylation of 1,3-diketones.

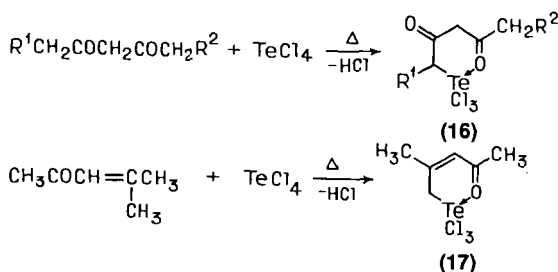


According to Morgan (25JCS2611) the formation of heterocycles **11** requires enolization of 1,3-diketones with the involvement of the terminal alkyl groups.



The reaction of 1,3-diketones with  $\text{TeCl}_4$  is thus viewed as the addition of the latter to a  $\text{C}=\text{C}$  double bond, although current understanding would be more compatible with direct electrophilic substitution at the  $sp^3$ -carbon center. A possible driving force for this reaction is the additional stabilization of the tellurium trichloride **16** by the  $\text{Te} \rightarrow \text{O}$  intramolecular coordination bond (83MI1). Such bonds are known to strongly stabilize organotellurium compounds, provided their spatial structure offers no constraints to the formation of the corresponding five- or six-membered rings [91JOM(402)331; 92MI1). This interpretation is in accord with the fact that the reaction of mesityl oxide with  $\text{TeCl}_4$  involves the terminal methyl group, resulting in the formation of compound **17** containing a strong intramolecular coordination  $\text{Te} \rightarrow \text{O}$  bond (83MI1).

On treatment with concentrated hydrochloric acid and aluminum amalgam, 1-telluracyclohexane-3,5-diones decompose with elimination of tellurium. Their chemical behavior is determined by the presence of the dicoordinate tellurium center and two carbonyl groups in their molecules. As cyclic diketones, compounds **12** readily form oximes and dioximes under treatment with hydroxylamine. The former reaction is preferably carried out in dilute acetic acid solution, whereas the latter is carried out in basic



media (24JCS1601; 25JCS797). As diorganyl tellurides, compounds **12** are susceptible to addition reactions. When reacting with halogens, they readily form  $\sigma$ -telluranes **11**, whereas main-group metal cations coordinate a molecule of **12**, giving rise to complexes in which the tellurium serves as a ligating atom. A well studied example is the complex of **12** and  $\text{HgI}_2$  (20JCS1456).

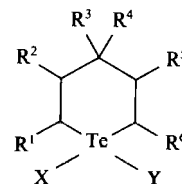
Some of the derivatives of 1-tellura-3,5-cyclohexane-3,5-dione **12** exhibit strong antimicrobial properties, but their application is prevented by high toxicity [23BJ30; 24BJ190, 24JCS1601, 24MI1; 25JCS2611; 26MI1; 44N(L)88]. Merocyanines containing 1-telluracyclohexane-3,5-dione fragments were found to be efficient photosensitizers [77JAP(K)76/136420, 77JAP(K)76/136722].

#### 4. Molecular and Crystal Structure of 1-Telluracyclohexane and Its Derivatives

Data concerning the X-ray-determined structures of derivatives of 1-telluracyclohexane of the general formula **18** are relatively scarce. Some data on bond lengths and valence angles in **18** are listed in Table I.

1-Telluracyclohexane-3,5-diones **18b–f** prefer the chair conformation, methyl groups taking an equatorial position. The  $\text{C}=\text{O}$  bond lengths span the range of 1.20–1.23 Å characteristic of the diketone tautomeric form. The dibenzo derivative of 1-telluracyclohexane, telluraxanthene, acquires the boat conformation (81ZSK106). In the crystal, the molecules of heterocycles **18b – f** are associated as a result of intermolecular  $\text{Te} \cdots \text{Te}$  interactions so that zigzag polymeric chains of tellurium atoms are formed. The intermolecular  $\text{Te} \cdots \text{Te}$  contacts (**18b** 3.95, 3.97, and 4.18 Å; **18e** 4.04 Å; **18c** 4.07 Å; **18f** 4.138 Å) are shorter than the sum of their van der Waals radii (4.4 Å), thus suggesting weak attractive  $\text{Te} \cdots \text{Te}$  interactions. These manifest themselves in the appearance of a yellowish color in compounds **18b,c, e,f** as crystals, whereas compound **18d** with an elongated  $\text{Te} \cdots \text{Te}$  contact (5.05 Å) is almost colorless. The intermolecular  $\text{Te} \cdots \text{Te}$  contacts (6.06 Å) are longest in phenoxatellurine (73JHC527),

TABLE I  
BOND LENGTHS (Å) AND VALENCE ANGLES IN COMPOUNDS **18**



	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	X	Y	Te—C	Te—X	Te—Y	C—Te—C angle (deg)	X—Te—Y angle (deg)	Reference
<b>a</b>	H	H	H	H	H	H	Br	C <sub>6</sub> H <sub>5</sub>	2.14	3.47–3.67	2.13	91.6	167.3	79CSC351
<b>b</b>	H	=O	H	H	=O	H	—	—	2.15	—	—	89.5	—	76JCS(D)2307
<b>b</b>	H	=O	H	H	=O	H	—	—	2.16	—	—	90.8	—	77AX(B)1469
<b>c</b>	CH <sub>3</sub>	=O	H	H	=O	CH <sub>3</sub>	—	—	2.195	—	—	89.7	—	77AJC487
<b>d</b>	H	=O	CH <sub>3</sub>	CH <sub>3</sub>	=O	H	—	—	2.168	—	—	86.4	—	77JCS(D)644
<b>e</b>	CH <sub>3</sub>	=O	CH <sub>3</sub>	H	=O	H	—	—	2.18	—	—	88.4	—	77JOM(125)125
<b>f</b>	CH <sub>3</sub>	=O	CH <sub>3</sub>	H	=O	CH <sub>3</sub>	—	—	2.18	—	—	89.3	—	77AX(B)2671
<b>g</b>	H	=O	H	H	=O	H	Cl	Cl	2.14	2.493	2.512	95.5	172.7	76JCS(D)2307

which is therefore the least colored among similar six-membered heterocyclic derivatives of dicoordinate tellurium.

1-Phenyltelluroniacyclohexane bromide **18a** possesses a distorted octahedral structure around the tellurium center with three relatively long Te·····Br intermolecular bonds (3.47–3.67 Å). The heterocycle has the chair conformation, with the phenyl group in an axial position. In the case of the  $\sigma$ -tellurane **18g** the tellurium atom occupies the center of a trigonal bipyramid; but owing to a weak secondary Te·····Cl interaction, its coordination polyhedron may also be regarded as octahedral.

1-Telluracyclohexane (as well as other six-membered saturated heterocycles) occurs, both in solution and in the crystalline state, in the chair conformation. Judging from the R values (67JA5921) ( $R = {}^3J_{\text{tr}}/{}^3J_{\text{cis}}$ ), the chair is slightly distorted in 1-chalcogenacyclohexanes ( $R = 2.61$ – $2.76$ ) as compared to that of pyran ( $R = 1.9$ ), but close to the ideal chair conformation of cyclohexane.

Of special interest are results of the dynamic NMR study of the conformational mobility of type-1 1-heteracyclohexanes (73JA4634) and their 3,5-naphtho analogs of type **4** (82CC333). Free energy barriers to ring inversion of these compounds are given in Table II. Values for compounds **1** decrease in the order O > S > Se > Te, whereas in their naphtho analogs, they increase in the same order.

Examination of  $^{13}\text{C}$  NMR spectra of type-1 heterocycles (76JA3778, 76JA3783) makes it possible to trace the effects of the nature of a group-16 (VIA) heteroatom on the chemical shifts of the ring carbon centers. Chemical-shift data for various 1-heteracyclohexanes, where the heteroatom is a group-6 element, are given in Table III.

The chemical shifts of the  $\alpha$ -carbon atoms are chiefly determined by the electronegativity of the heteroatom. An increase in the coordination number of the chalcogen center (in chalcogenium salts,  $\sigma$ - and  $\pi$ -telluranes) leads to a downfield shift of the  $\alpha$ -carbon atom signals. The

TABLE II  
FREE ENERGY BARRIERS TO RING INVERSION OF COMPOUNDS **1** and **4**

Structural type, heteroatom	Coalescence temperature (°C)	$\Delta G^\ddagger$ (kcal/mol)	Structural type, heteroatom	Coalescence temperature (°C)	$\Delta C^\ddagger$ (kcal/mol)
<b>1</b> , O	–61	10.3	<b>4</b> , O	—	6.3
<b>1</b> , S	–81	9.4	<b>4</b> , S	–118	7.4
<b>1</b> , Se	–105	8.2	<b>4</b> , Se	–108	7.6
<b>1</b> , Te	–119	7.3	<b>4</b> , Te	–97.5	8.0

TABLE III  
CHEMICAL SHIFTS IN  $^{13}\text{C}$  NMR SPECTRA OF COMPOUNDS



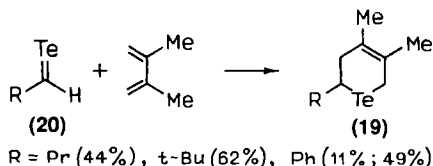
M	Solvent	Chemical shifts ( $\delta$ , ppm)			M	Solvent	Chemical shifts ( $\delta$ , ppm)		
		$\alpha$ -C	$\beta$ -C	$\gamma$ -C			$\alpha$ -C	$\beta$ -C	$\gamma$ -C
O	—	68.0	26.6	23.6	SeBr <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	51.2	20.9	22.9
S	—	29.3	28.2	26.9	TeBr <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	36.9	20.3	25.9
Se	—	20.2	29.1	28.4	SI <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	33.3	25.9	—
Te	—	-2.1	29.9	30.9	SeI <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	29.7	25.7 <sup>a</sup>	26.0 <sup>a</sup>
SO(mixt)	CDCl <sub>3</sub>	49.0	19.3	25.2	TeI <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	33.2	21.4	25.5
SO(ax)	CD <sub>2</sub> Cl <sub>2</sub>	45.1	15.5	24.7	HS <sup>+</sup> FSO <sub>3</sub> <sup>-</sup>	HSO <sub>3</sub> F	31.2	24.1	21.8
SO(eq)	CD <sub>2</sub> Cl <sub>2</sub>	52.1	23.3	24.7	HSe <sup>+</sup> FSO <sub>3</sub> <sup>-</sup>	HSO <sub>3</sub> F	41.2	23.8	22.5
SeO(mixt)	CH <sub>2</sub> Cl <sub>2</sub>	42.1	18.6	26.3	HTe <sup>+</sup> FSO <sub>3</sub> <sup>-</sup>	HSO <sub>3</sub> F	24.0 <sup>a</sup>	25.0 <sup>a</sup>	25.8 <sup>a</sup>
Se(ax)	CH <sub>2</sub> Cl <sub>2</sub>	39.4	16.8	25.1	CH <sub>3</sub> S <sup>+</sup> I <sup>-</sup>	H <sub>2</sub> O	37.8	20.5	22.7
SO <sub>2</sub>	CDCl <sub>3</sub>	52.6	25.1	24.3	CH <sub>3</sub> Se <sup>+</sup> I <sup>-</sup>	H <sub>2</sub> O	34.1	20.5	23.9
SBr <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	34.7	22.9	27.6	CH <sub>3</sub> Te <sup>+</sup> I <sup>-</sup>	H <sub>2</sub> O	—	20.7	27.7

<sup>a</sup> Assignment are not clear.

most significant shifts are observed in covalent trigonal-bipyramidal  $\sigma$ -chalcogenuranes ( $M = \text{SeBr}_2, \text{TeBr}_2, \text{TeI}_2$ ); these shifts are much smaller if interaction of chalcogenacyclohexanes with halogens results not in the formation of  $\sigma$ -chalcogenuranes ( $M = \text{SBr}_2, \text{SI}_2, \text{SeI}_2$ ), but in the formation of charge-transfer complexes **1** with their respective halogens. For more information on the relationships between the structure of the products of coupling 1-chalcogenacyclohexanes (in general diorganyltellurides) with halogens and the nature of the latter, Lambert *et al.* see (72JA8172). The  $^{13}\text{C}$  chemical shifts of  $\gamma$ -carbon atoms also correlate with the electronegativity of the heteroatom, but, unlike those of the  $\alpha$ -carbon atoms, they move upfield with increasing electronegativity of the heteroatom. The chemical shifts of the  $\beta$ -carbon atoms in the ring are affected, apart from the electronegativity of heteroatomic groups in position 1, also by the orientation (axial or equatorial) of the substituents at the heteroatom. An illustrative example is given by conformers of 1-thiacyclohexane oxide (Table III). The higher the electronegativity of the heteroatom, the greater are the upfield chemical shifts of the  $\beta$ -carbon atoms of 1-heteracyclohexanes, but these shifts are smaller than those of the  $\gamma$ -carbon atoms. In general, the effect of the electronegativity of the heteroatomic groups in position 1 on the chemical shifts of ring carbon atoms is as follows:  $\alpha$  (50 ppm per unit of electronegativity)  $> \gamma$  (5 ppm)  $> \beta$  (2.5 ppm) (76JA3778).

### B. 1-TELLURACYCLOHEX-3-ENE AND ITS DERIVATIVES

A general method for the preparation of the title compounds has been developed only recently. Triply substituted 1-telluracyclohex-3-enes **19** were synthesized in moderate yields by the Diels–Alder reaction of telluroaldehydes **20** with 2,3-dimethylbutadiene (89AG181, 89JA8749).

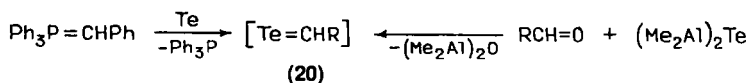


In contrast to their sulfur and selenium analogs, telluroaldehydes **20** and telluroketones have not yet been isolated in the pure state and are known in the form of their complexes with transition-metal ions (see, for instance, 89JA8749). Therefore in the reaction with 2,3-dimethylbutadiene these were used *in situ*. To generate **20** two different approaches were

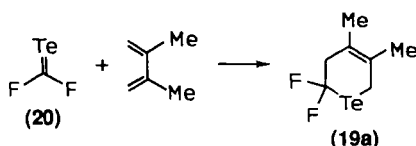


employed. One of these is based on the reaction of a phosphonium ylide with elemental tellurium (89AG181), whereas the second involves the reaction of bis(dimethylaluminum) telluride (obtained through interaction of bis(trimethyltin) telluride with trimethylaluminum) (89JA8749). From comparison of the yields of compounds **19** attained with the use of these two methods, 11% and 49%, respectively, the latter is preferable.

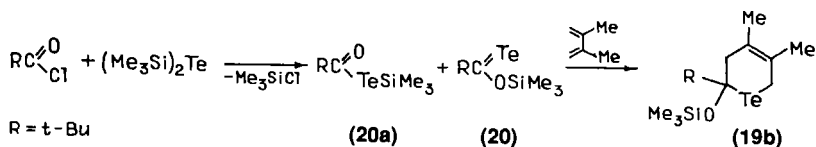
The reaction based on the use of bis(dimethylaluminum) telluride was also employed to generate telluroketones. Through coupling with adamantanone and bicyclo[3.3.1]nonan-9-one and subsequent treatment of the products with cyclopentadiene, the corresponding seven-membered heterocycles were prepared in 52–55% yields (89JA8749). Recently, the peculiar  $\pi 2 + \pi 4$  reaction of 2,3-dimethylbutadiene with the difluorotelluroketone (generated by the reaction of  $(\text{CF}_3\text{Te})\text{Hg}$  with  $\text{Et}_2\text{AlI}$ ) has been described; this reaction afforded the heterocycle **19a** in a very low (1–2%) yield [93JCS(D)2547]. The yield can be somewhat increased when  $\text{Me}_3\text{Sn-TeCF}_3$  is used as the precursor of the difluorotelluroketone.



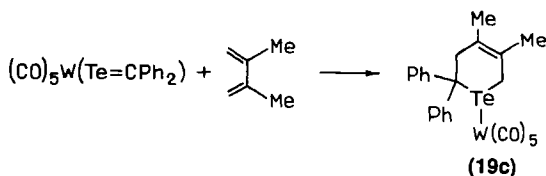
Less studied is another approach to derivatives of 1-tellurocyclohex-3-ene **19** by which the first representatives of this heterocyclic system were obtained. It is also based on the Diels–Alder reaction, where trimethylsilyl telluropivaloate **20** is used as the dienophile (87CC820; 92M14). Compound **20** is formed, along with its isomer **20a**, upon treatment of pivaloyl chloride with bis(trimethylsilyl) telluride, the **20/20a** ratio being approximately 2 : 1.



The complex of **19** with tungsten pentacarbonyl has been prepared in 12% yield by reaction of 2,3-dimethylbutadiene with benzotellurophenone coordinated to tungsten pentacarbonyl [86JOM(299)C7].



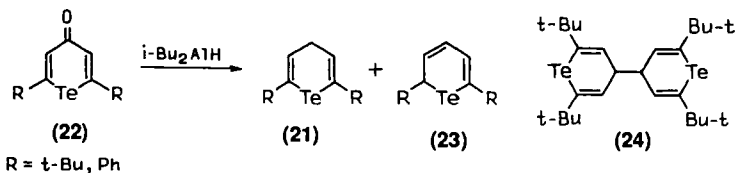
Reactions of derivatives of **19** have not yet been studied. The only information available on their properties is that these are comparatively



inert to air and moisture, but readily eliminate tellurium in acidic media (89JA8749).

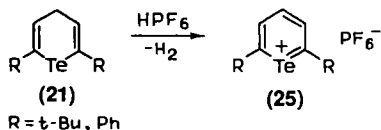
### C. SYNTHESIS AND REACTIONS OF 1-TELLURACYCLOHEXA-2,5-DIENE AND ITS DERIVATIVES

1-Telluracyclohexa-2,5-dienes **21** have been prepared in yields higher than 60% by the reduction of 1-telluracyclohexa-2,5-dien-4-ones **22** with diisobutylaluminum hydride (88MI2). Along with the targeted heterocycles **21**, their isomers, 1-telluracyclohexa-2,4-dienes **23**, have been found in small amount (yields 3–5%) among the products. On reduction of 2,6-di-*tert*-butyl-1-telluracyclohexa-2,5-dien-4-one, the dimer **24** is formed in 29% yield, indicating a radical mechanism.

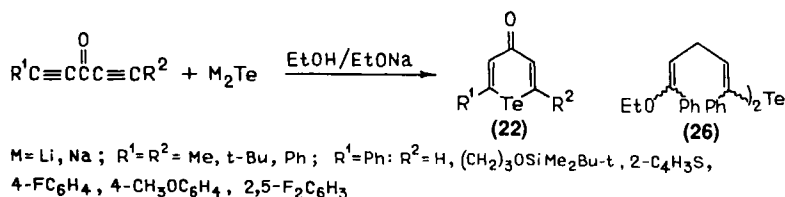


Whereas no other methods of synthesis of **21** and its derivatives are currently known, the nucleophilic addition of telluride anion to 1,5-diorganylpentadi-1,4-ynes may be considered a promising approach, based on the finding that sodium telluride reacts smoothly with monosubstituted alkynes, giving rise to divinyltellurides (89MI1).

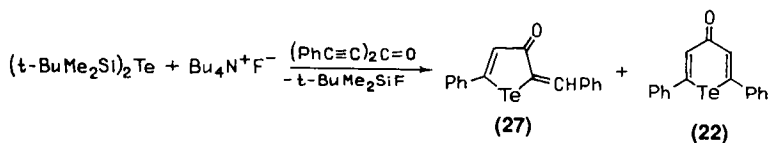
Reactions of 1-telluracyclohexa-2,5-dienes **21** have been little studied. When heated with HPF<sub>6</sub> in acetic acid, compounds **21** eliminate dihydrogen and convert to tellurapyrylium salts **25**. The yields (73–83%) are higher than those of the same reaction with the oxygen, sulfur, and selenium analogs of **21** (88MI2).

Reactions of the keto derivatives of **21**, 1-telluracyclohexa-2,5-dien-4-

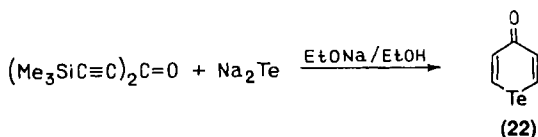
ones **22** have been studied in more detail. Both symmetric **22** and nonsymmetric **22a** compounds were obtained in 12–60% yields by the nucleophilic addition reaction of telluride anion to penta-1,4-diyn-3-ones in a strongly basic medium (solution of EtONa in ethanol). The reactions of elemental tellurium with NaBH<sub>4</sub> in ethanol (85T4853; 86MI2; 92MI3) or LiEt<sub>3</sub>BH in 8tetrahydrofuran (82JOC1968, 82JOC5235; 83TL539; 85T4853; 87JOC3662) served as the source of telluride anion. The yields of non-symmetrically substituted 1-telluracyclohexa-2,5-dien-4-ones **22** are usually lower than those of their symmetric counterparts **22**. No formation of by-product was observed. The only exception is the case of 1,5-diphenylpenta-1,4-diyn-3-one (R = Ph) where noncyclic telluride **26** was formed in low yield (10%) along with the main product **22** (82JOC1968).



Likewise, no products of the anti-Michael addition were found in the reaction above. Compound **27** was obtained in 28% yield in the case of 1,5-diphenylpenta-1,4-diyn-3-one (82JOC1968) when bis(*tert*-butyldimethylsilyl) telluride was used as the source of telluride anion. Heterocycle **22** (R<sup>1</sup> = R<sup>2</sup> = Ph) is also formed (in 19% yield).

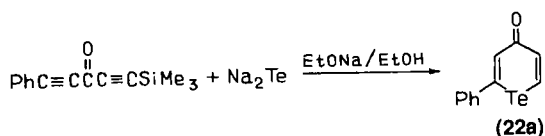


The attempts to apply both of the above-described reactions for the preparation of the parent heterocycle **22** (R<sup>1</sup> = R<sup>2</sup> = H) with the use of penta-1,4-diyn-3-one were only partially successful. The yields of **22** (R<sup>1</sup> = R<sup>2</sup> = H) were lower than 5%, the main products being unidentified oligomers (92MI3). The first synthesis of **22** (R<sup>1</sup> = R<sup>2</sup> = H) of preparative significance was when 1,5-bis(trimethylsilyl)penta-1,4-diyn-3-one was the

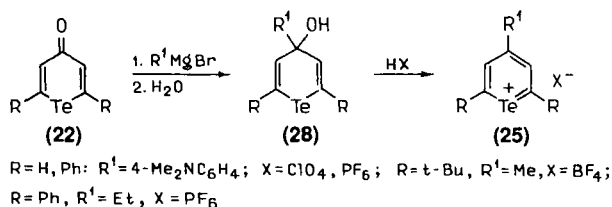


precursor. By coupling it with sodium telluride (from Te and  $\text{NaBH}_4$ ) in ethanol in the presence of  $\text{EtONa}$ , the heterocycle **22** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ) was prepared in 38% yield (92MI3). Desilylation of the initial ketone is suggested to precede the cyclization stage.

The addition of telluride anion to 1-(trimethylsilyl)penta-1,4-diyn-3-ones apparently represents a general method for the preparation of 2-substituted 1-telluracyclohexa-2,5-dien-4-ones **22** (92MI3). In actual fact, the reaction of 1-(trimethylsilyl)-5-phenylpenta-1,4-diyn-3-one with telluride anion affords **22** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ) in 38% yield, whereas only 12% of this compound is attained in the reaction with 1-phenylpenta-1,4-diyn-3-one (87JOC3662).

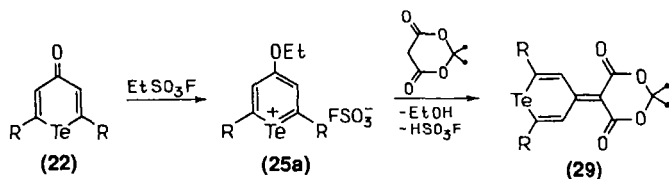


Tellurapyrones **22** display reactions characteristic of both cyclic tellurides and unsaturated carbonyl-containing compounds. It has been pointed out that these are readily reduced to 1-telluracyclohexa-2,5-dienes **21** by diisobutylaluminum hydride (88MI1). Reacting with arylmagnesium bromides, compounds **22** form the corresponding heterocyclic alcohols **28**, which were not isolated but were directly converted to tellurapyrylium salts under the action of strong mineral acids (82JOC5235; 88MI3; 92MI2, 92MI3).



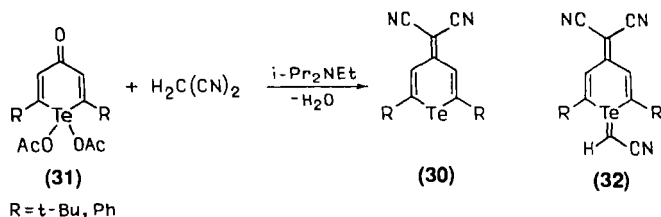
Treatment of heterocyclic ketones **22** with ethyl fluorosulfate leads to tellurapyrylium salts **25a** (82JOC5235; 87JOC2123), and interaction with Meldrum's acid produces compounds **29**.

Compound **22** readily reacts with 4-methylpyrylium and other 4- and 2-methylchalcogenapyrylium salts (see Section II,H,2d). However, in contrast to 2,6-diphenylthiopyran-4-one, which reacts with dicyanomethane smoothly in acetic anhydride, tellurapyrones **22** are inert to this reagent. To provide for the synthesis of tellurapyranylideneomalodinitriles **30**, whose formation might be expected in such a reaction, the derivatives of **22**,

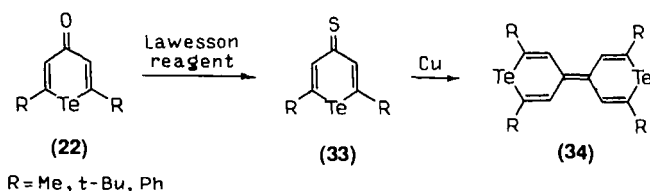


1,1-diacetoxy-1-telluracyclohexa-2,5-dien-4-ones **31**, should be used, the reaction being promoted by diisopropylethylamine (87JOC2123). The mechanism of the reaction remains uncertain and the yields of compounds **30** are rather low (24 and 29%). Along with **30** ( $\text{R} = \text{Ph}$ ) and other compounds of unidentified structure, **32** was isolated in 11% yield as a product of this reaction. Apart from diacetates **31**, no other 10-Te-4 telluranes of type **30** are known to enter into the reaction with dicyanomethane.

Tellurapyrones **22** when treated with Lawesson's reagent convert to thiones **33** in almost quantitative yields (82JOC1146; 83TL539; 85T4853). The latter compounds serve as synthons for the preparation of 1-tellurapyran-4-yl-4H-tellurapyrones **34** which are obtained in 22–80% yields by a refluxing toluene solution of the thiones **33** in the presence of copper powder (82JOC11146; 83TL539; 85T4853).

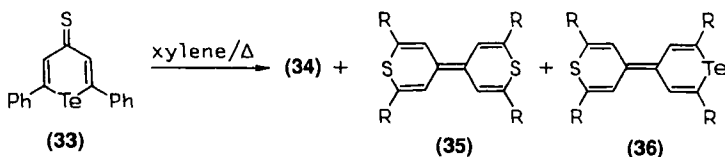


It is worth noting that compounds **34** ( $\text{R} = \text{Ph}$ ) are formed in trace amounts (in less than 1% yield) by self-condensation of thiones **33** ( $\text{R} = \text{Ph}$ ) in xylene. The main products are **35** and **36** in the ratio 45:55 (82JOC1146). Their formation is due to the thermal extrusion of a sulfur atom from **33** and the subsequent substitution of a tellurium heteroatom in the six-membered ring. It was found that refluxing a solution of **34** ( $\text{R} = \text{Ph}$ ) in xylene with the addition of elemental sulfur leads

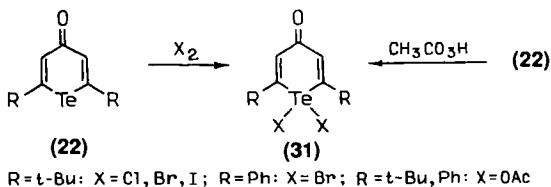


to the formation of **35** in high yield. The same type of transformations of tellurium-containing heterocycles to their sulfur analogs is also known for phenoxatellurines (85MI1) and 2-phenylbenzotellurazole (89KGS989).

Like other dicoordinate tellurium compounds, 1-telluracyclohexa-2,5-dien-4-ones **22** smoothly add halogens (chlorine, bromine, and iodine) affording  $\sigma$ -telluranes **31** in rather high yields. When treated with a peroxy acid, compounds **22** form 1,1-diacetoxy derivatives **31** (87JOC2123). 1-Tellurapyranylideneomalondinitriles **30** undergo similar transformations.



However, oxidative addition reactions of **22** with  $\text{NaIO}_4$ ,  $m\text{-ClC}_6\text{H}_4\text{CO}_3\text{H}$ ,  $N$ -chlorosuccinimide, and  $\text{tert-BuOCl}$  do not lead to the expected diorganyl tellurium oxides,  $\sigma$ -telluranes, or telluronium salts as was the case with acyclic diorganyl tellurides (79MI1; 80JOC274; 84JOC4819; 85TL895). Instead, insoluble compounds of unidentified structure were isolated in these reactions of **22** (87JOC2123).

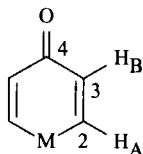


4-Tellurapyranyl-4*H*-tellurapyrones **34** with TCNQ form charge-transfer complexes with a composition of 1 : 1 ( $\text{R} = \text{Ph}$ ), 1 : 2, and 2 : 3 ( $\text{R} = \text{Me}$ ). No individual crystalline complex was isolated in the reaction of TCNQ with 2,2',6,6'-tetra-*tert*-butyltellurapyranyl-4*H*-tellurapyrone (83TL539). The oxidation potentials and electric conductivities of these complexes were measured, the latter being found to be relatively low as compared to most other charge-transfer complexes formed by TCNQ (83TL539; 85T4853).

A comparative study of spectral characteristics and X-ray-determined structural parameters in the series of 1-chalcogenacyclohexa-2,5-dien-4-ones has been undertaken (92MI3). Some of the results are represented by the data in Table IV.

As seen from the data in Table IV, for the tellurapyrones the chemical

TABLE IV

<sup>1</sup>H AND <sup>13</sup>C NMR, IR, AND UV SPECTRAL PARAMETERS OF 1-CHALCOGENOCYCLOHEXA-2,5-DIEN-4-ONES<sup>a</sup>

M	$\delta$ , ppm (CDCl <sub>3</sub> )					$\nu_{C=O}$ , cm <sup>-1</sup>	$\lambda_{max}$ , nm ( $\epsilon$ ) (CH <sub>2</sub> Cl <sub>2</sub> )
	H <sub>A</sub>	H <sub>B</sub>	C <sub>2</sub>	C <sub>3</sub>	C <sub>4</sub>		
S	7.47	7.02	137.7	131.7	179.8	1610	297(11,000)
Se	8.21	7.17	138.8	132.6	181.0	1585	310(16,500)
Te	8.71	7.31	136.8	129.3	184.7	1560	344(20,000)

<sup>a</sup> From Detty and Gibson (92MI2).

shifts of  $\alpha$ -hydrogen and  $\alpha$ -carbon ring atoms are found, respectively, in the lowest and highest fields in a series of chalcogenapyrones of type **22**. A gradual decrease in the  $\nu_{C=O}$  frequencies, as well as a steady bathochromic shift in the long-wavelength UV-absorption band, is apparent in the order: thia-, seleno-, tellurapyrones.

According to X-ray structural data (92MI3), 1-telluracyclohexa-2,5-dien-4-one is planar. No substantial intermolecular interaction between different molecules of **22** (R = H) are observed in crystal. The Te $\cdots$ Te (4.11Å) and Te $\cdots$ O (3.22Å) intermolecular distances are rather close to the values of the sum of their respective van der Waals radii.

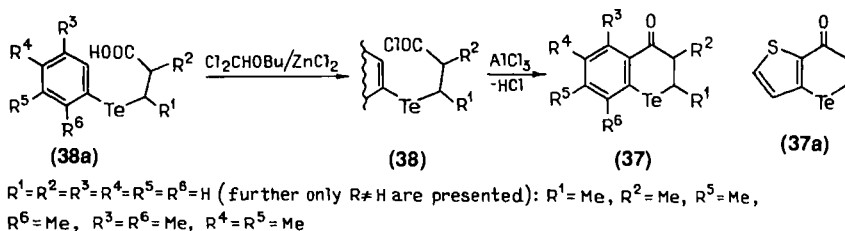
## D. DERIVATIVES OF TELLURACHROMANE

### 1. Synthesis

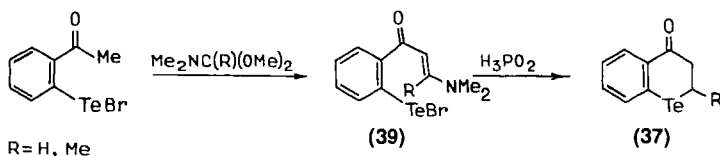
Whereas the preparation of telluraisochromane has been documented [43N(L)749; 45JCS37], tellurachromane has not yet been obtained. Derivatives of tellurachromane, tellurachromanones **37**, were prepared in highly varying yields (from 2% to 60%) by cyclization of acyl chlorides **38** in CH<sub>2</sub>Cl<sub>2</sub> at -78°C catalyzed by AlCl<sub>3</sub> (75JHC423; 90UPI). The same method has been applied to the syntheses of naphtho[1,2-*b*]tellurachromanone (75JHC423) and heterocycle **37a** [83JOM(258)163].

The tendency of dicoordinate tellurium compounds to undergo oxida-

tive addition reactions prohibits using such reagents as  $\text{PCl}_5$  or  $\text{SOCl}_2$  for the preparation of type-**38** acyl chlorides. In the presence of these reagents, **38** or their precursors containing dicoordinate tellurium centers convert to the corresponding insoluble tellurium dichlorides. For this reason, acyl chlorides **38** and their analogs are usually obtained by treatment of tellurium-containing carbonic acids **38a** with dichloromethyl alkyl ethers in the presence of  $\text{ZnCl}_2$ . The initial acids **38a** were synthesized in high yields through either alkylation of sodium aryltelluroates with  $\beta$ -halogenopropionic acids (70BSB353; 75JHC423) or nucleophilic addition of aryltelluroate anions to the double bond of acrylic acid (88ZOB717; 90UPI).



Another approach to tellurachromanones **37** involves reduction of  $\beta$ -(*o*-bromotelluroaryl)enamines **39** with excess  $\text{H}_3\text{PO}_2$  [79PS73; 81JOM(208)11]. The yields are reasonably high (60–65%). The initial compounds **39** are accessible by virtue of the readily occurring reaction of 2-bromotellurenylacetophenone with dimethylformamide (dimethylacetamide) dimethylacetals, falling into the range of 45–80%.

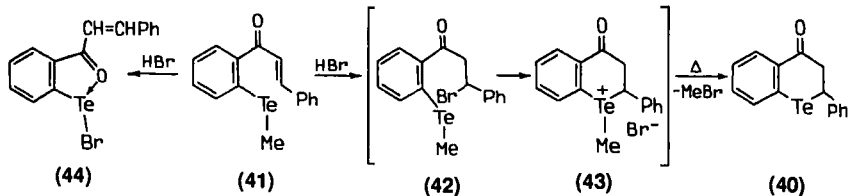


The weakness of the  $\text{C}_{\text{aliph}}\text{—Te}$  bonds relative to the bonds formed by other chalcogen atoms (90MI1) accounts for the limited applicability of a number of methods frequently used for the preparation of sulfur- and selenium-containing heterocycles to their tellurium analogs. The attempts to obtain tellurachromanone and some of its derivatives by pyrolysis of  $\beta$ -(*o*-carboxyphenyltelluro)propionic acid as well as those related to a Dieckmann condensation of its diester failed due to cleavage of the  $\text{C}_{\text{aliph}}\text{—Te}$  bond and resulted in the formation of ditellurosalicyclic acid (75JHC423). Also, cyclization of the  $\beta$ -phenyltelluropropionic acid or its



esters catalyzed by PPA under conditions similar to those used to obtain selenachromanones (64BSB483) is not an effective route to tellurachromanone because of decomposition of the starting acid with extrusion of tellurium.

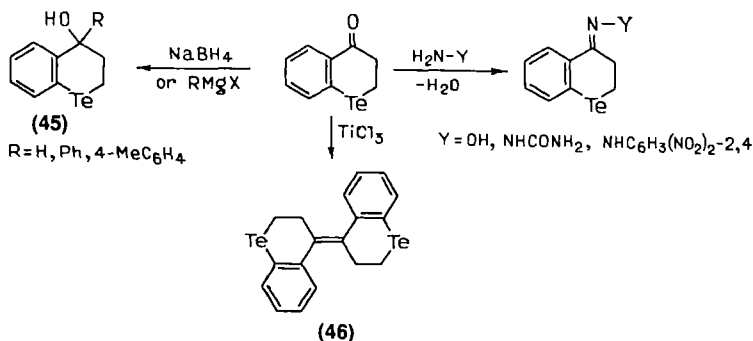
Although the acyl chloride of 3-phenyltelluro-2-methylpropanoic acid when treated with  $\text{AlCl}_3$  readily undergoes a cyclization reaction to afford 2-methyltellurachromanone, the attempts to extend the cyclization to 3-phenyltelluro-2-phenylpropionic acid in order to obtain telluraflavanone **40** were unsuccessful (71BSB669). However, the method employed earlier to prepare a selenium analog of **40** (62CB1237) proved suitable. The heterocycle **40** was obtained in 20% yield upon heating 2-cinnamoylphenylmethyl telluride **41** in acetic acid saturated with hydrogen bromide (71BSB669). A possible mechanism involves formation of the intermediate **42** and its subsequent cyclization to the telluronium salt **43**. The latter eliminates  $\text{CH}_3\text{Br}$  [the reaction is known to occur readily for many other telluronium salts (74MI1; 83MI2)] when converting to **40**. A by-product is 2-cinnamoylphenyltellurenyl bromide **44**. Such protodetelluration reactions are known for various *o*-alkyltellurophenylcarbonyl compounds (90MI1; 92MI1). The driving force is determined by the strong stabilization of the reaction products due to intramolecular coordination  $\text{O} \leftarrow \text{Te}$  bonds.



## 2. Reactions

The reactions of tellurachromanones are associated with its two basic reaction centers: the carbonyl group and the dicoordinate tellurium heteroatom (75JHC423; 90UP1). As a cyclic ketone, compound **40** reacts with hydroxylamine, semicarbazide (90UP1), and 2,4-dinitrophenylhydrazine (75JHC423; 90UP1). When reacting with Grignard reagents or  $\text{NaBH}_4$ , it forms tellurachromanols **45**. Reaction of tellurachromanone with titanium trichloride results in deoxygenation and the formation of 4,4'-bis(tellurachromanylidene) **46**, for which a transconfiguration is assumed to be energetically preferable (90UP1) (Scheme 2).

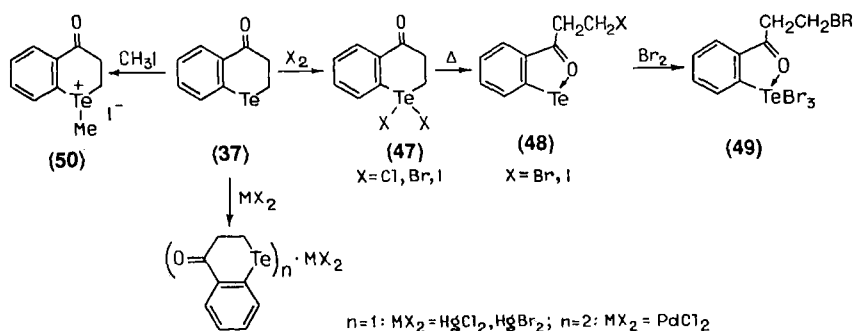
As a cyclic telluride, tellurachromanone is prone to oxidative addition reactions which increase the coordination number of the tellurium atom to 3 or 4 (90UP1). Under mild conditions tellurachromanone adds halogens,



SCHEME 2

giving rise to heterocyclic 10-Te-4 telluranes **47** in very high yields. In contrast to thiachromanone which affords 3-bromothiachromanone upon treatment with bromine (25CB1612), tellurachromanone on short heating forms 1,1-dibromotellurachromanone **47** (X = Br). Prolonged heating of **47** with an excess of bromine leads to the rearrangement of the initially formed **47** to 2-( $\beta$ -bromopropionyl)phenyltellurenyl bromide **48**, followed by its oxidation to 2-( $\beta$ -bromopropionyl)phenyltellurium tribromide **49** (90UP1). Upon treatment with methyl iodide, tellurachromanone forms the corresponding telluronium salt **50** (75JHC423; 90UP1). The tellurium atom also serves as a donor center in a complexation reaction between **37** and Hg(II) or Pd(II) salts (90UP1) (Scheme 3).

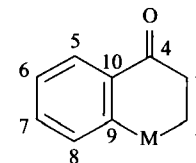
1,1-Dihalogenotellurachromanones **47** on heating (20–30 hours) in CHCl<sub>3</sub>, PhBr, or PhNO<sub>2</sub> also undergoes rearrangement to form **48** (X = Br, I) (90UP1, 90ZOB2764). In the case of 1,1-dichlorotellurachromanone **48** (X = Cl) the rearrangement gives 2-acryloylphenyltellurenyl chloride **51**, most probably from the initially formed 2-( $\beta$ -chloropropionyl)-



SCHEME 3

$R^1 = R^2 = R^3 = R^4 = R^5 = H$  (further only  $R \neq H$  are presented):  $R^1 = Me$ ;  $R^2 = Me$ ;  $R^3 = Me, Ph, 4-MeC_6H_4$ ;  $R^4 = Me$ ;  $R^5 = Me$

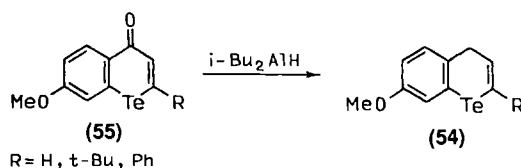
TABLE V  
SPECTRAL CHARACTERISTICS AND DIPOLE MOMENTS OF CHALCOGENACHROMANONES **52**



Heteroatom M	Chemical shifts ( $\delta$ , ppm)									$\nu_{\text{C=O}}$ , $\text{cm}^{-1}$ ( $\text{CCl}_4$ )	$\lambda_{\text{max}}$ , nm	$\mu$ , D
	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10			
O	67.1	37.9	191.3	127.3	121.3	135.8	118.0	160.2	121.5	1701	319	2.26
S	24.1	37.4	191.2	126.9	122.8	131.0	125.4	140.1	128.9	1688	346	2.00
Se	18.3	40.2	194.7	127.4	125.6	132.8	130.0	133.3	136.7	1685	355	2.07
Te	-4.0	40.4	195.4	129.2	125.4	131.2	134.1	117.8	136.1	1679	375	2.24

ture was applied for the preparation of **53a** [83JOM(258)163]. The tellurachromanoles possessing aryl groups in position 4 undergo the dehydration reaction even under the action of a mild dehydrating agent such as  $\text{Al}_2\text{O}_3$  (90UP1).

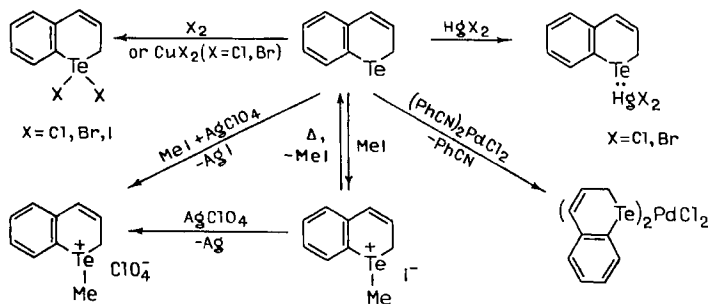
4*H*-Tellurachromenes **54** were obtained in 75–85% yields by reduction of the corresponding tellurachromones **55** with diisobutylaluminum hydride (88MI2). In the earlier report on this reaction (83JA883), the products were erroneously referred to as “tellurachromanols.”



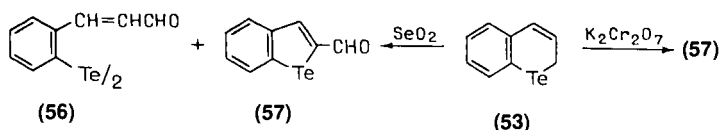
## 2. Reactions of 2*H*-Tellurachromenes

2*H*-Tellurachromenes are susceptible to the reactions typical of dicoordinate tellurium compounds. These are summarized in Scheme 4 (88KGS1050; 90UP1).

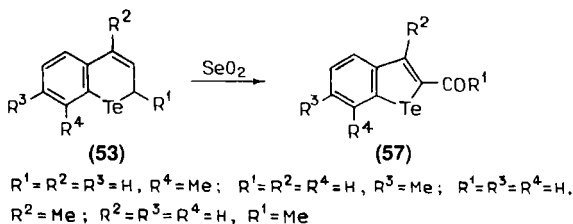
Whereas 2*H*-thia- and 2*H*-selenachromenes (69BSB459) may be oxidized by chromic anhydride in pyridine to the corresponding coumarines, attempts [83JOM(258)163] to apply this reaction to tellurachromenes failed. Another oxidant,  $\text{Ti}(\text{OAc})_3$ , gives bis[2-(3'-propen-2'-al-1')phenyl] ditelluride **56** in 75% yield [83JOM(258)163]. When  $\text{SeO}_2$  is employed to oxidize 2*H*-tellurachromene in the molar ratio 1 : 1, compound **56** is formed along with 2-formylbenzo[*b*]tellurophene **57**. When excess  $\text{SeO}_2$  is used, the only product is **57** [83JOM(258)163], as is also the case for the oxidation of 2*H*-tellurachromene by  $\text{K}_2\text{Cr}_2\text{O}_7$  in acetic acid (88KGS1050).



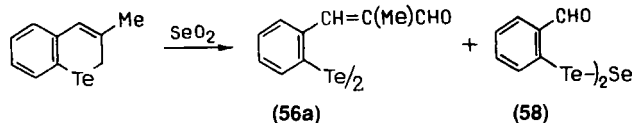
SCHEME 4



The formation of derivatives of 2-formylbenzotellurophene is characteristic of the oxidation of 2*H*-tellurachromenes **53** possessing substituents in positions 4, 7, and 8. The oxidation of 2-methyl-2*H*-tellurachromenes affords 2-acetylbenzo[*b*]tellurophenes **57** ( $R^1 = \text{Me}$ ) in 10–15% yields [83JOM(258)163].

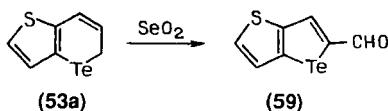


The presence of a 3-methyl group in **53** changes the reaction course. When the oxidant  $\text{SeO}_2$  is used in more than twofold excess relative to 3-methyl-2*H*-tellurachromene, bis[2-(3'-propene-2'-methyl-1'-al)phenyl]-ditelluride **56a** is formed in 60% yield. When a smaller relative amount of  $\text{SeO}_2$  is used in this reaction, aldehyde **56a** is formed along with the product of selenium insertion into the Te—Te bond, **58** (in 15% yield [83JOM(258)163]).

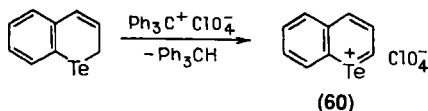


The first representative of a new heterocyclic system, tellura[3,2-*b*]thiophene **59** has been prepared by oxidation of the thiophenoannelated 2*H*-tellurapyrane **53a** [83JOM(258)163].

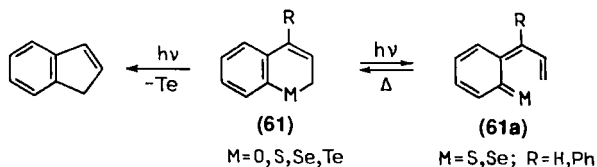
The treatment of 2*H*-tellurachromene with an equimolar amount of trityl perchlorate in trifluoroacetic acid leads to tellurachromylium perchlorate **60** obtained in low yield (86KGS1570; 88KGS1050) (see Section II,H,1).



In contrast to *2H*-chromenes **61** ( $M = O$ ) (66JA5931), thia- ( $M = S$ ) (68JPC997) and selenachromenes **61** ( $M = Se$ ) (73TL2007), on UV irradiation, undergo reversible valence isomerization to quinoneallydines **61a**; *2H*-tellurachromene **61** ( $M = Te$ ) eliminates tellurium and converts to indene under the same conditions (90UP1).



*4H*-Tellurachromones **54** give tellurochromylium salts with  $HPF_6$ . No other transformations of **54** have been described in the literature.



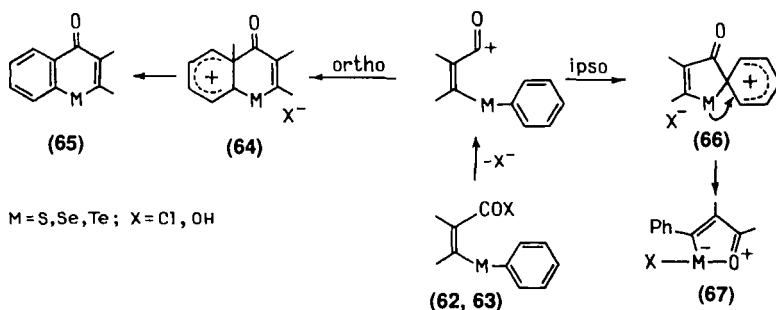
## F. TELLURACHROMONE, ITS DERIVATIVES, AND ANALOGS

In this section we consider the methods of synthesis as well as the structure and reactions of tellurachromones, telluraflavones (2-phenyl-substituted tellurachromones) and telluracoumarines.

### 1. Synthesis

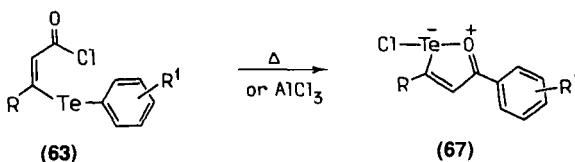
Two of the most important methods of synthesizing tellurachromones and telluraflavones are (1) the intramolecular Friedel–Crafts cyclization of either  $\beta$ -(aryltelluro)propenoyl chlorides (88JA883; 88MI4) or the corresponding acids (88JA883) and (2) the intramolecular cyclization of  $\beta$ -(*o*-bromotelluroaroyl)enamines under the action of  $H_3PO_2$ . The former method well illustrates the peculiarities in reactivity of organotellurium compounds as compared with their sulfur and selenium analogs (90MI1).

The electrophilic cyclization of  $\beta$ -(arylchalcogeno)propenoic acids **62** and acyl chlorides **63** may occur in two different ways. Whereas *ortho* acylation involving formation of the intermediate **64** gives rise to the six-membered heterocycles, chalcogenachromones (flavones) **65**, *ipso* acylation is accompanied by formation of the typical  $\sigma$ -complex **66**, which transforms to the five-membered heterocycle, 1,2-oxachalcogenolium chloride **67**.



The extreme cases are  $\beta$ -arylthio- and  $\beta$ -aryltelluropropenoyl chloride (or the corresponding acids). The former compounds, regardless of the nature of the substituents in the aryl ring, undergo only the *ortho* acylation that results in the formation of thiachromones **65** (M = S) [57JA5311; 59JA4931; 64LA(680)40; 67ZOB367; 83JA883]. Quite the reverse, *ipso* acylation and subsequent formation of the heterocycles **67** represents the preferred reaction pathway for various  $\beta$ -aryltelluropropenoyl chlorides (83JA883; 88MI4). Such a course of reaction is due to the enhanced polarizability of tellurium and its relatively low (compared to the higher chalcogens) electronegativity. The selenium analogs of the  $\beta$ -arylthio- and  $\beta$ -aryltelluropropenoyl chlorides **63** (M = Se) undergo the cyclization reaction in either direction, forming, depending on the substitution in the selenoaryl ring, heterocycles **65** (M = Se) (65AG913; 66BSB260; 80JOC4611) or **67** (M = Se). In some cases both of these heterocycles were formed simultaneously (83JA883).

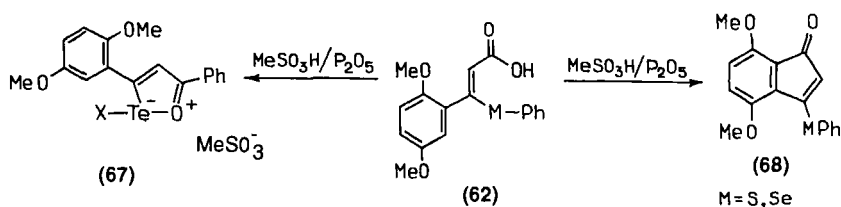
High yields of 1,2-oxatellurolium chlorides **67** were achieved in the thermal- or  $\text{AlCl}_3$ -catalyzed rearrangements of  $\beta$ -(aryltelluro)propenoyl chlorides (83JA883; 88MI4).



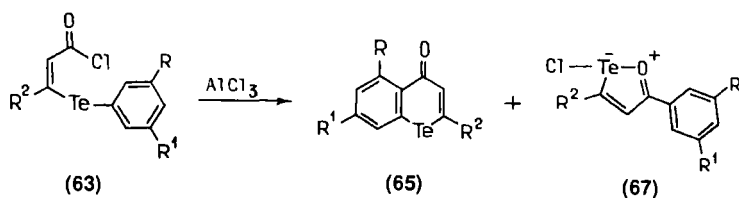
The peculiar reactivity of organotellurium compounds manifests itself also in the course of the cyclization reaction of  $\beta$ -chalcogenoaryl cinnamic acids **62** (X = OH). Whereas the thio and seleno derivatives form on treatment with  $\text{MeSO}_3\text{H}/\text{P}_2\text{O}_5$  benzocyclopentenones **68** (80JOC4611), their tellurium-containing analogs, undergo a different ring-closing reaction that leads to 1,2-oxatellurolium methanesulfonate **67**.

By suitable substitution it is possible to activate the *ortho* positions of





the tellurium-substituted aryl groups in **62** to electrophilic attack, and thereby channel the cyclization reaction of **62** to the formation of the tellurachromones and telluraflavones **65**. Depending on the number and nature of the substituents  $\text{R}$ , compounds **65** and **67** may be obtained in a widely variable ratio.



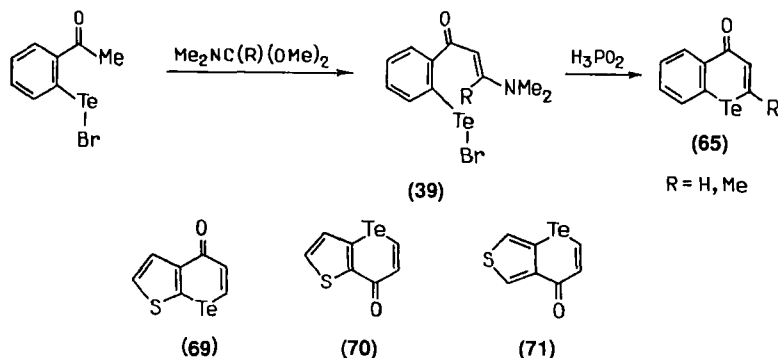
	R	R <sup>1</sup>	R <sup>2</sup>	% <b>65</b>	% <b>67</b>
<b>a</b>	H	F	Ph	~6	~94
<b>b</b>	H	F	F	18	~80
<b>c</b>	H	OCH <sub>3</sub>	Ph	92 <sup>a</sup>	4
<b>d</b>	OCH <sub>3</sub>	OCH <sub>3</sub>	Ph	90	0
<b>e</b>	H	OCH <sub>3</sub>	H	67	0
<b>f</b>	H	OCH <sub>3</sub>	CH <sub>3</sub>	67	0
<b>g</b>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	74	0
<b>h</b>	OCH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	67	0
<b>i</b>	H	OCH <sub>3</sub>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	44 <sup>b</sup>	0
<b>j</b>	H	OCH <sub>3</sub>	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	68 <sup>b</sup>	0
<b>k</b>	H	OCH <sub>3</sub>	2,5-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	50 <sup>b</sup>	0

<sup>a</sup> Along with **65**, isomeric telluraflavone **65a** has been isolated in 4% yield.

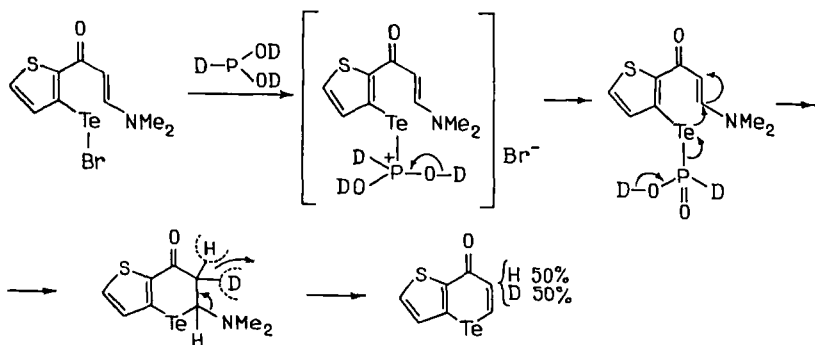
<sup>b</sup> The compounds **67** also formed in this reaction as by-products (yields are about 5%).

For the synthesis of those tellurachromones and telluraflavanones that do not contain strong electron-releasing substituents in positions 5 and 7 of **62**, the method proved suitable based on different synthons— $\beta$ -(*o*-bromotelluroaroyl)enamines **39** [79PS73; 81JOM(208)11]. Compounds **39** were obtained in 45–80% yields by coupling *o*-bromotellurenyl acetophenone with dimethyl acetals of *N,N*-dimethylformamide or *N,N*-dimethylacetamide. Reduction of enamines **39** with  $\text{H}_3\text{PO}_2$  gives rise to

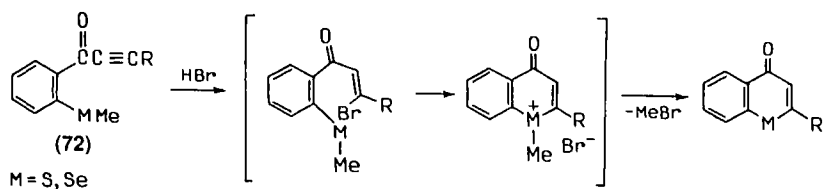
tellurachromones **65** in 45% yield. The reaction was extended to the preparation of tellurapyrones with fused thiophene rings **69–71** (79PS73).



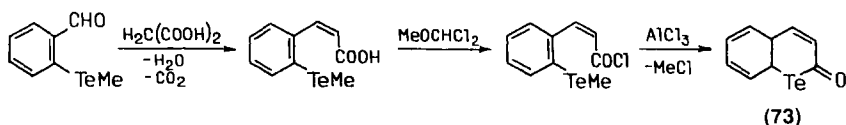
Renson proposed the following mechanism of conversion of enamines **39** to tellurachromones, which accounted for the deuterium content in the cyclization products [81JOM(208)11].



In 1985 a new approach to the synthesis of chalcogenachromones was developed that involved a ring-closing reaction of *o*-alkylchalcogenaphenyl ethynyl ketones **72** under the action of a 30% solution of hydrogen bromide in acetic acid [85JOM(287)81]. The mechanism of this reaction implies the addition of  $\text{HBr}$  to the triple bond and subsequent intramolecular alkylation at the chalcogen center with elimination of  $\text{CH}_3\text{Br}$ . No limitations seem to exist for the utilization of this method of synthesis of tellurachromones and telluraflavones; however, the reaction was not tested because the tellurium analogs of compounds **72** have not yet been described.

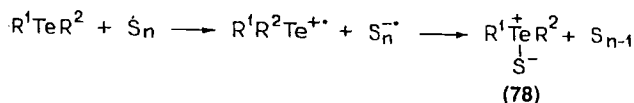


The method employed earlier to obtain selenacoumarin (69BSB449) was also extended to the preparation of its tellurium analog **73**. 2-Methyltellurocinnamic acid was converted to its acyl chloride, which was cyclized to **73** in 20% yield under the action of  $\text{AlCl}_3$  (84JHC1281).

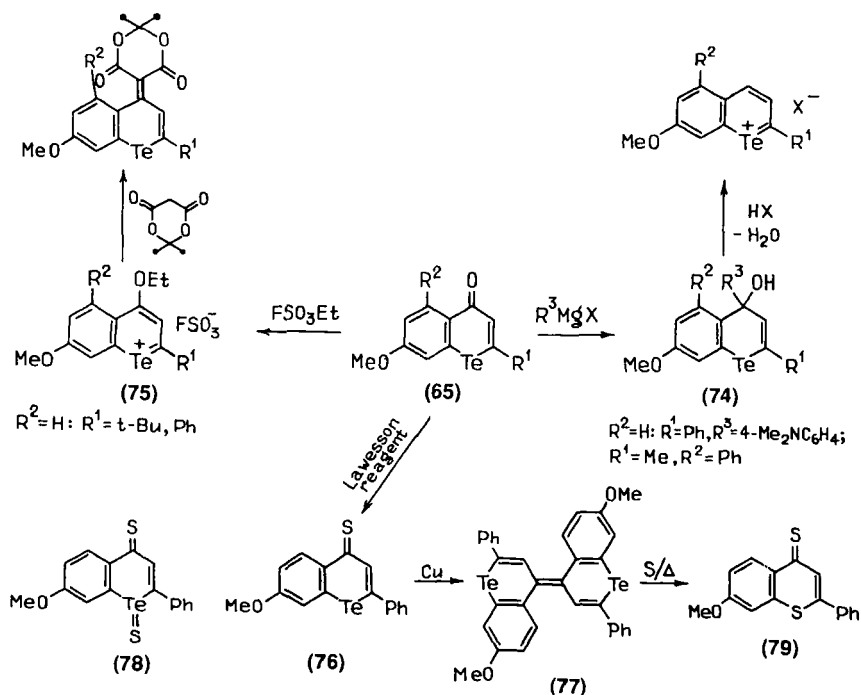


## 2. Reactions

Like 1-telluracyclohexa-2,5-dien-4-ones **22**, tellurachromones and telluraflavones are inert to  $\text{NaBH}_4$ , but are reduced by diisobutylaluminum hydride to 4*H*-tellurachromenes in 75–85% yields. Compounds **65** react with Grignard reagents, giving rise to alcohols **74** (83JA883). These are alkylated by ethyl fluorosulfate at the carbonyl oxygen, giving rise to tellurachromylum salts **75** (83JA883; 87JOC2123; 88M14) and under treatment with Lawesson's reagent convert to thiones **76** (82JOC1146; 88M14) which form dimers **77** under the action of copper powder (82JOC1146). The thione **78** (82JOC1146) was obtained in relatively low (24%) yield by treatment of telluraflavone with two equivalents of Lawesson's reagent. Compound **78** remains the only known representative of tellurosulfides, the sulfur analogs of the well studied telluroxides (88M15). It has been suggested that the formation of tellurosulfide **78** follows the electron-transfer reaction pathway shown below (82JOC1146).



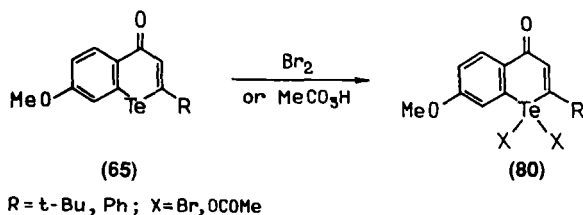
Refluxing a xylene solution of **77** with a large amount of sulfur leads not only to replacement of the tellurium atom by a sulfur exchange reaction, but also to the transformation of the dipyranylidene structure of **77** to thione **79** (82JOC1146). Another route to **79** is by prolonged refluxing of a toluene solution of **78**. Scheme 5 features the above reactions.



SCHEME 5

Tellurachromones and telluraflavones readily convert to the cyclic 10-Te-4 telluranes **80** on reaction with bromine or peracetic acid (87JOC2123).

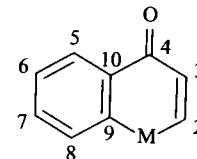
In contrast to 1,1-diacetoxytellurapyrones **31**, compounds **80** ( $\text{X} = \text{OCOMe}$ ) react with malonodinitrile in the presence of diisopropylethylamine to give the corresponding flavones in yields higher than 50% (87JOC2123).



### 3. Spectral Characteristics of Tellurachromones

A comparative study of the spectral properties and dipole moments of a series of chalcogenachromones **81** has been carried out [81JOM(208)23; 83SA(A)693]. An excerpt of the data obtained is given in Table VI.

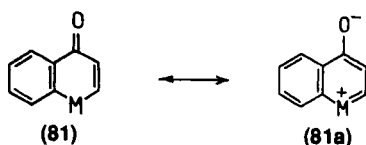
TABLE VI  
SPECTRAL PARAMETERS AND DIPOLE MOMENTS OF CHALCOGENACHROMONES **82**<sup>a</sup>



Heteroatom M	Chemical shifts ( $\delta$ , ppm)											$\nu_{\text{C=O}}$ , $\text{cm}^{-1}$ ( $\text{CCl}_4$ )	$\lambda_{\text{max}}$ , nm	$\mu$ , D
	H-2	H-3	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10			
O	7.78	6.24	155.8	113.3	177.9	126.1	125.6	134.1	118.5	155.6	125.3	1669	217, 237, 295, 301	3.46
S	7.74	6.91	138.2	127.1	180.0	129.1	126.3	131.8	128.2	137.9	132.8	1636	220, 245, 285, 334	3.48
Se	8.14	7.10	137.6	128.4	181.2	128.7	127.8	131.3	130.1	133.3	136.5	1629	220, 222, 252, 348	3.47
Te	8.61	7.38	134.6	134.3	185.5	128.9	126.4	131.5	132.3	124.2	136.6	1625	201, 261, 388	3.65

<sup>a</sup> From Dereu *et al.* [81JOM(208)23] and Baiwir *et al.* [83SA(A)693].

The gradual decrease in the  $\nu_{C=O}$  frequencies of compounds **81** in the sequence  $O > S > Se > Te$  attests to the steady growth of polarity of the compounds, i.e., an increase in relative contribution of the dipolar structure **81a** to the resonance hybrid. The trend in increasing dipole moments of these compounds when passing from chromone to tellurachromone is in accord with this conclusion.



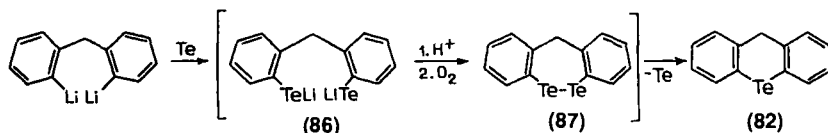
## G. TELLURAXANTHENE AND ITS DERIVATIVES

### 1. Synthesis

Telluraxanthene **82** has been prepared by two methods. First the synthesis was accomplished by the intramolecular electrophilic cyclization of 2-benzylphenyltellurium trichloride **83** and subsequent reduction of the 10,10-dichlorotelluraxanthene **84** thus formed (78KGS1567; 80KGS1342). The trichloride **83** was obtained by addition of chlorine to di(2-benzylphenyl) ditelluride **85** (78KGS1567; 80KGS1342) or by coupling 2-benzylphenyltrimethylsilane with  $TeCl_4$  (80KGS1342). The cyclization of 2-benzylphenyltellurium trichloride to **84** occurs smoothly when an *o*-dichlorobenzene (or 1,2,4-trichlorobenzene) solution of **83** is heated at 60–70°C in the presence of one equivalent of  $AlCl_3$ . Without  $AlCl_3$ , the yields of telluraxanthene are very low, even when the reaction is carried out at elevated temperature. The role of  $AlCl_3$  in the cyclization reaction thus consists in the enhancement of the electrophilicity of the  $TeCl_3$  substituent caused by coordination. The adduct may be assigned the structure  $[RTeCl_2]^+[AlCl_4]^-$  (80KGS1342) by analogy with the ionic structure of the product of the interaction between tellurium tetrachloride and aluminum trichloride  $[TeCl_3]^+[AlCl_4]^-$  (71MI1). Under analogous conditions, 2-benzylphenyltellurium tribromide does not undergo cyclization due to a considerable decrease in the electrophilicity of  $TeHal_3$  groups on passing from chlorine to bromine (61T219). On the other hand, for the heteroatomic analogs of **83**, 2-(phenylamino)phenyltellurium trichloride (89H1007), 2-(phenoxy)phenyltellurium trichloride (26JCS223), and 2-(phenylthio)phenyltellurium trichloride (60T15) containing a strongly electron-releasing substituent atom positioned *ortho* to the  $TeCl_3$  group, the cyclization

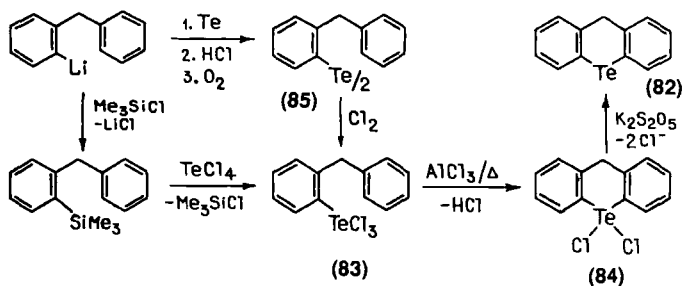
proceeded without promotion by  $\text{AlCl}_3$ , although at the rather high temperatures of 150–250°C. Scheme 6 features the reactions discussed.

The second method employed for the synthesis of telluraxanthene is similar to that widely used for the preparation of various tricyclic heterocycles containing one or two heteroatoms. It is based on the interaction of 2,2'-dilithiodiphenylmethane with powdered tellurium, by which reaction telluraxanthene **82** has been prepared in 50% yield [81JOM(205)167]. The reaction apparently proceeds through the intermediate bis(tellurophenolate) **86** which is oxidized to the heterocyclic ditelluride **87**. The latter compound eliminates tellurium from its sterically strained seven-membered ring and converts to telluraxanthene. This mechanistic scheme seems to be corroborated by the observation that the treatment of lithioarenes  $\text{ArLi}$  usually ends in the formation of diarylditellurides  $\text{Ar}_2\text{Te}_2$  (74MI1; 83MI2).

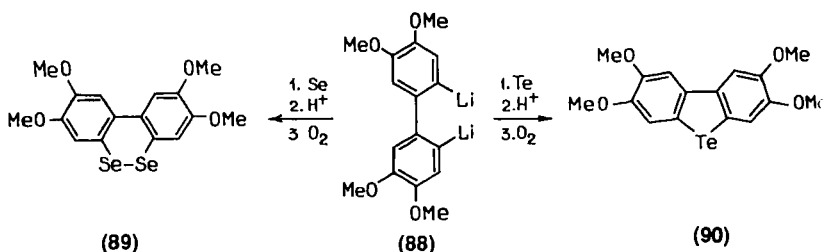


More evidence for the increased steric strain caused by the voluminous ditelluride unit encased in a ring may be found in the reaction of the derivative of *o,o'*-dithiodiphenyl **88** with chalcogens (84JHC413). Whereas the treatment of **88** with selenium allows the formation of the six-membered heterocycle **89** (although in a very low yield of 4%), the reaction with tellurium results in dibenzotellurophene **90** formed, most probably, through extrusion of tellurium from the cyclic ditelluride similar to **89**.

Although the first method is a four-step sequence of reactions and the second one is a one-step reaction, the yields of telluraxanthene are

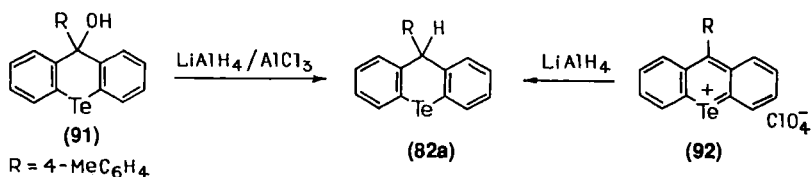


SCHEME 6



approximately equal. Owing to the fact that the 2-bromobenzylbenzene starting material for the first method is more accessible than that (2,2'-dibromodiphenylmethane) for the second method, preference is given to the former.

9-Substituted telluraxanthenes have scarcely been studied. 9-(*p*-Tolyl)-telluraxanthene has been prepared in high yield by the reduction of 9-(*p*-tolyl)telluraxanthenol **91** with LiAlH<sub>4</sub> in the presence of anhydrous AlCl<sub>3</sub> and also by the reduction of 9-(*p*-tolyl)-10-telluroniaanthracene **92** with LiAlH<sub>4</sub> (81KGS343).

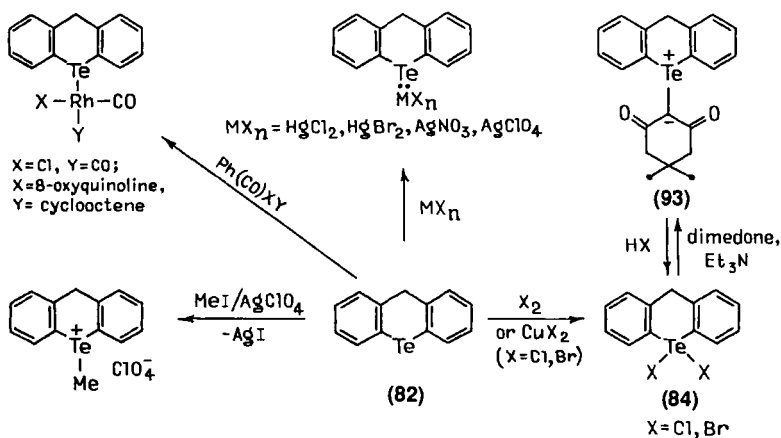


## 2. Reactions

The reactions of telluraxanthene across the dicoordinate tellurium center closely resemble those of the tellurium-containing heterocycles described above. Some of the  $\sigma$ -telluranes **84** (X = F, OCOF<sub>3</sub>) were prepared from the ylide **93** [formed from 10,10-dibromotelluraxanthene **84** (X = Br) and dimedone in the presence of triethylamine by analogy with the method developed for the synthesis of acyclic tellurium ylides (75ZOB2563; 77ZOB2232)] treated with the corresponding acids. With inorganic salts and rhodium carbonyls, telluraxanthene forms stable complexes (84MI1). Scheme 7 portrays the reactions of telluraxanthene.

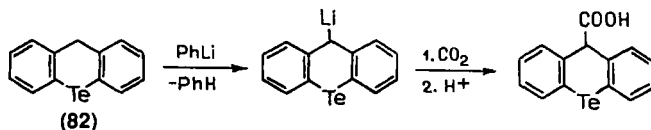
Treatment of telluraxanthene with phenyllithium in benzene gives 9-lithiotelluraxanthene in 60% yield (80KGS1342). Reaction with trityl perchlorate converts **82** into 10-telluroniaanthracene perchlorate (Section





SCHEME 7

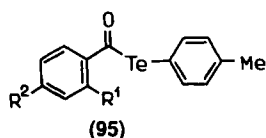
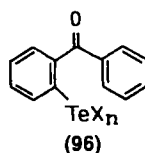
II,H,1). The methylene group of telluraxanthene can be easily oxidized to a carbonyl group, telluraxanthone being the product.



### 3. Synthesis and Reactions of Telluraxanthone

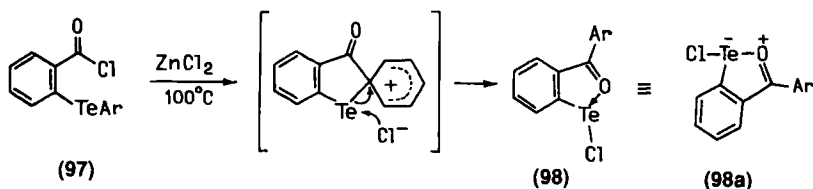
Several reactions suitable for the synthesis of thia- and selenaxanthone and their derivatives were found not to be adaptable for the preparation of the tellurium analogs. Thus, attempts to synthesize telluraxanthones **94** via photocyclization of the telluroesters **95** failed, although the selenium and sulfur analogs of **95** convert to chalcogenaxanthones under UV irradiation. Instead, UV irradiation of solutions of **95** results in a complex mixture of compounds originating from the cleavage of the  $\text{Te}-\text{C}$  bonds [78JOM(154)263, 78TL613; 81JOM(205)167]. Equally unsuccessful were attempts to effect cyclization of 2-(halogenotelluro)benzophenones [81JOM(205)167].

We have already considered (Section II,F) the rearrangement of  $\beta$ -(aryltelluro)propenoyl chlorides **63** to 1,2-oxatellurolium chlorides **67**, which was studied in detail by Detty (83JA875, 83JA883). This type of rearrangement was described for the first time by Renson for 2-chlorocarbonyldiphenyl telluride [75CS(A)117] and then extended to acyl chlorides

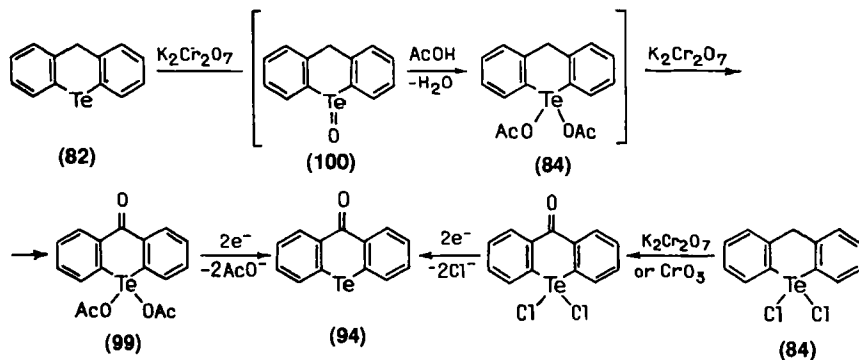

 $R^1 = \text{H}; R^2 = \text{H, OMe}$ 
 $R^2 = \text{H}; R^1 = \text{Cl, SMe, SO}_2\text{Me, OMe}$ 

 $\text{X} = \text{Br, Cl}; n = 1, 3$ 

of other *o*-aryltellurobenzoic acids **97** (78T655). On heating at 100°C compounds **97** do not form telluraxanthenes, as might be expected by analogy with the behavior of their oxygen and sulfur congeners, but rather rearrange to *o*-aroylbenzenetellurenyl chlorides **98**. Owing to the strong intramolecular coordination inherent in these compounds, their structure may be equally correctly formulated as **98a**, i.e., as benzo-1,2-oxatellurolium chlorides.

An analogous rearrangement was found with selenium analogs of **97**, but not with those of sulfur [75CS(A)117].


 $\text{Ar} = \text{Ph, 4-MeC}_6\text{H}_4, 2\text{-C}_4\text{H}_5\text{S}$ 

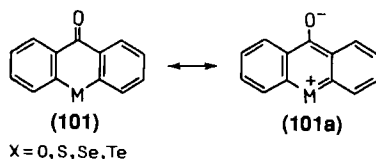
In fact, the only known method of synthesis of telluraxanthone **94** is that based on the oxidation of telluraxanthene (80KGS1342) or 10,10-dichlorotelluraxanthene [80KGS1342; 81JOM(205)167] with potassium dichromate (80KGS1342) or chromic anhydride [81JOM(205)167] in acetic



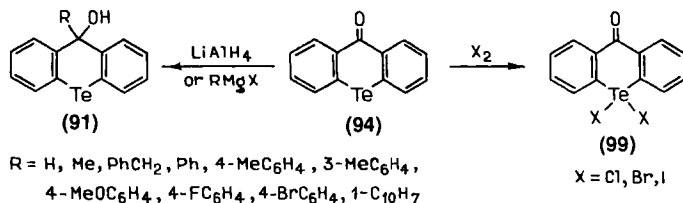
acid. Apparently, under the action of strong oxidants telluraxanthene initially forms the corresponding oxide **100**, which interacts, like similar diaryl telluroxides (75ZOB2562; 77ZOB2536), with excess acetic acid giving rise to telluraxanthene 10,10-diacetate **84** ( $X = \text{OCOMe}$ ). At the next step of the reaction the methylene group of **84** is oxidized. By reduction of the resulting diacetates **99** with  $\text{K}_2\text{S}_2\text{O}_5$ , telluraxanthone is obtained in 75% yield.

The first report [79CZ(103)265] on the preparation of telluraxanthone from 2,2'-diazobenzophenone and sodium telluride (in 2% yield) is apparently ambiguous, since the melting point of the product obtained ( $202^\circ\text{C}$ ) and assigned to **94** differs sharply from that of genuine telluraxanthone ( $115^\circ\text{C}$ ) (80KGS1342).

The observed trend in the frequencies of the bond stretching vibrations in the series of xanthone ( $1660\text{ cm}^{-1}$ ), thioxanthone ( $1645\text{ cm}^{-1}$ ) (73KGS990), selenaxanthone ( $1620\text{ cm}^{-1}$ ) (70BSB511), and telluraxanthone ( $1590\text{ cm}^{-1}$ ) (80KGS1342) is similar to that observed for chromone and chalcogenachromones **81**. It serves as evidence for the growing contribution of polar-resonance-type **101a** structures on going from **101** ( $M = \text{O}$ ) to **101** ( $M = \text{Te}$ ).

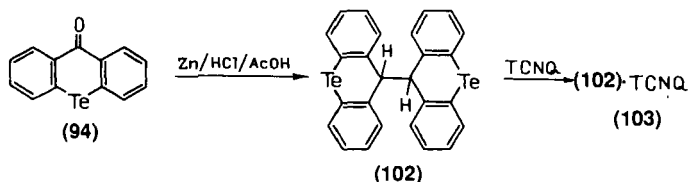


Telluraxanthone readily adds chlorine, bromine, and iodine to form 10,10-dihalogenotelluraxanthenes **99** (80KGS1342). Through coupling with  $\text{LiAlH}_4$  or Grignard reagents, telluraxanthone can be transformed to the respective 9-telluraxanthenols **91** in 57–90% yields (80KGS274; 81KGS343).



The peculiar chemical behavior of telluraxanthone is manifested by its reaction with zinc powder in a mixture of acetic acid and hydrochloric acid (81ZSK106). When xanthone is reduced under the above conditions,

bis(9-xanthylidene) is formed (79JA665). In contrast to this, telluraxanthone produces 9,9'-bis(telluraxanthenyl) **102** with a single C—C bond between the two tricyclic moieties. The structure of compound **102** has been proved by X-ray analysis (81ZSK106).



With TCNQ in a solution of dimethylformamide (DMFA) the dimer **102** forms the 1 : 1 charge-transfer complex **103** (83IZV690). The crystal structure of **103** is represented by stacked alternate layers of the molecules of TCNQ and **102**, the latter adopting a nonplanar conformation. The average distance between the layers is 3.37 Å. The electrical conductivity measured for a monocrystal of the charge-transfer complex of **102**—TCNQ is  $10^{-7} \text{ ohm}^{-1}\text{cm}^{-1}$ .

#### 4. Molecular and Crystal Structure of Telluraxanthene and 9,9'-Bis(telluraxanthenyl)

The molecule of telluraxanthene **82** has a butterfly conformation with the dihedral angle between the planar fragments of  $129.6^\circ$ . In contrast to derivatives of 1-telluracyclohexane, which possess the chair conformation (Section II,A,4), the tellurium-containing six-membered ring of **102** adopts the boat conformation. The Te—C bond lengths and the C—Te—C valence angle are of the usual values for the organotellurium compounds. Figure 1 features the geometry of the tellurium-containing six-membered ring of **82** as found by the X-ray structural study (81ZSK106).

In the crystal, the molecules of 9,9'-bis(telluraxanthenyl) **102** adopt the

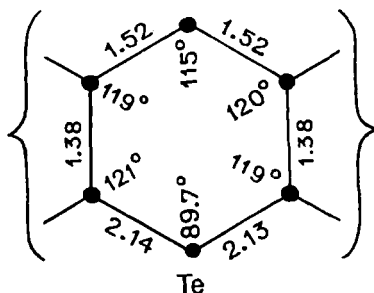


FIG. 1. Bond lengths and angles of the telluraxanthene molecule.

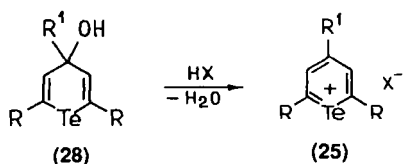
transconformation, their tricyclic moieties being markedly flattened (the dihedral angles are  $138.8^\circ$  and  $140.5^\circ$ ) as compared to **82**. The C—C bond is elongated to  $1.574 \text{ \AA}$  (81ZSK106).

## H. TELLURAPYRYLIUM CATIONS AND BENZOANNELATED DERIVATIVES

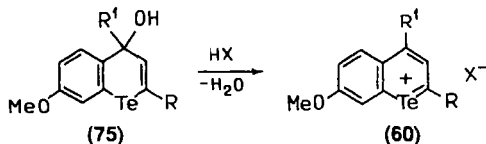
The first compound containing the tellurapyrylium ring, 10-telluroni-anthracene perchlorate was synthesized in 1980 (80KGS274). Before long a broad series of the derivatives of tellurapyrylium and tellurachromylium cations was described.

### 1. Synthesis

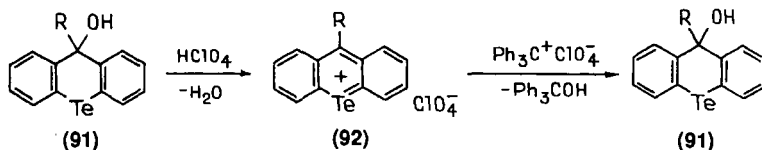
The methods of synthesis of tellurapyrylium salts **25** (82JOC5235; 86MI2; 88MI3) and their benzo derivatives, tellurachromylium **60** (83JA883) and telluraxanthylum salts **92** (80KGS274; 81KGS343), are common to those employed in the synthesis of their oxygen-containing heterocyclic analogs. These include the treatment of the respective alcohols with strong mineral acids ( $\text{HClO}_4$ ,  $\text{HPF}_6$ ,  $\text{HSO}_3\text{F}$ ) or trityl perchlorate



$\text{R} = t\text{-Bu}$ ;  $\text{R}' = \text{Me}$ ,  $4\text{-Me}_2\text{NC}_6\text{H}_4$ ;  $\text{R} = \text{Ph}$ ;  $\text{R}' = \text{Et}$ ,  $4\text{-Me}_2\text{NC}_6\text{H}_4$ ;  
 $\text{X} = \text{ClO}_4$ ,  $\text{BF}_4$ ,  $\text{PF}_6$



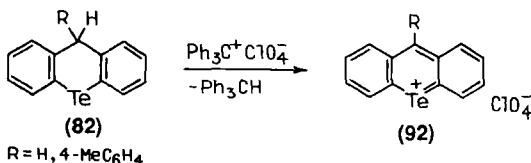
$\text{R} = \text{Me}$ ;  $\text{R}' = \text{Ph}$ ;  $\text{R} = \text{Ph}$ ;  $\text{R}' = 4\text{-Me}_2\text{NC}_6\text{H}_4$



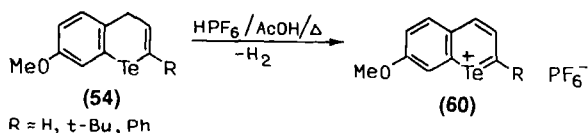
$\text{R} = \text{H}$ ,  $\text{Me}$ ,  $\text{PhCH}_2$ ,  $\text{Ph}$ ,  $4\text{-MeC}_6\text{H}_4$ ,  $3\text{-MeC}_6\text{H}_4$ ,  $4\text{-MeOC}_6\text{H}_4$ ,  $4\text{-FC}_6\text{H}_4$ ,  
 $4\text{-BrC}_6\text{H}_4$ ,  $1\text{-C}_{10}\text{H}_7$

to split out hydroxide anion from the cyclic moiety. The yields of the salts of tellurium-containing heterocyclic cations are in the range of 44–98%.

A less common approach to the tellurachromylium and telluraxanthylum cations is based on dehydrogenation of 2*H*-tellurachromene **53** (86KGS1570) and telluraxanthenes **82** (81KGS343) with trityl perchlorate.

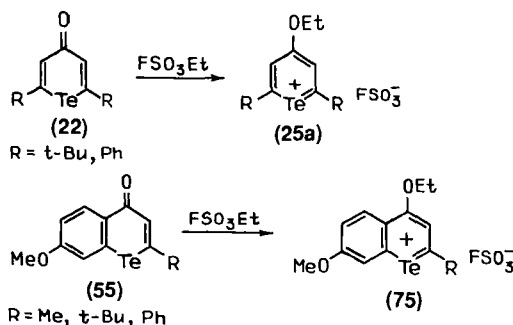


Recently it was reported that the salts of tellurapyrylium **25** and tellurachromylium **60** cations can be obtained in high yields (60–85%) by heating, respectively, 4*H*-tellurapyranes **21** and 4*H*-tellurachromenes **54** with  $\text{HPF}_6$  in acetic acid (88MI2).



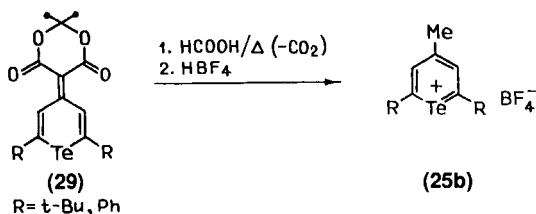
The reaction is known also for the oxygen, sulfur, and selenium analogs of compound **54** ( $\text{R} = t\text{-Bu}$ ). Interestingly, the yields of hexafluorophosphates of the heterocyclic cations gradually decrease in this reaction in the order: Te (85%) > Se (64%) > S (59%) > O (22%).

Alkylation of tellurapyrones **22** (82JOC5235; 86MI2; 87JOC2123) and tellurachromones **55** (83JA883; 88MI4) with ethyl fluorosulfate occurred at the carbonyl oxygen atom of 4-alkoxy derivatives of **25a** and **75**.

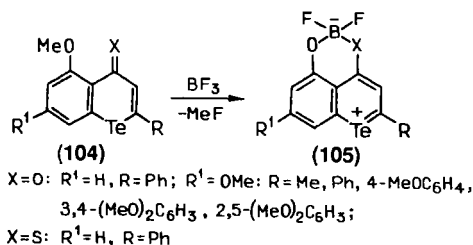


Good yields (60–87%) of the 4-methyltellurapyrylium tetrafluoroborates **25b** were achieved when tellurapyranylidenes **29** were heated with formic

acid and then treated with  $\text{HBF}_4$  to replace formate anions (82JOC5235; 86MI2).



The difluoroboronate chelate complexes of the derivatives of tellurachromones **104** ( $\text{X} = \text{O}$ ) and tellurathiochromone **104** ( $\text{X} = \text{S}$ ), which may be viewed as the corresponding tellurachromylum zwitterions **105**, were prepared through the demethylation reaction of the 5-methoxy derivatives **104** under the action of the complex  $\text{BF}_3\text{-Et}_2\text{O}$  (88MI4).

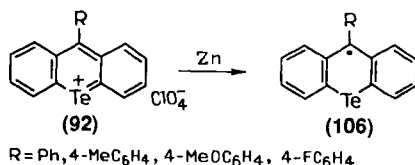


## 2. Reactions

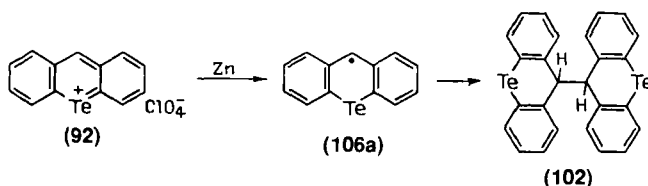
The reactions of the dibenzo derivative of the tellurapyrylium cation, 10-telluroniaanthracene, were studied in considerable detail. In general, the reactions of tellurapyrylium salts are similar to those of their oxygen, sulfur, and selenium analogs. The peculiar chemical behavior caused by the presence of a tellurium center is most clearly manifested in the reaction of tellurapyrylium cations bearing dimethylamino groups with halogens.

**a. Reduction.** Reduction of telluraxanthylum salts **92** with  $\text{LiAlH}_4$  leads to telluraxanthenes **82** (81KGS343; see also Section II,G,1). When zinc powder is used as a reducing agent in tetrahydrofuran (80KGS1421; 88KGS1196) or benzene (88KGS1196), the perchlorates **92** produce free radicals **106**, which are the first representatives of stable tellurium-containing radicals.

The radicals **106** ( $\text{R} = \text{Ph}$ ) display well-resolved ESR spectra (88KGS1196), as is also the case with their oxygen (68JPC3641), sulfur

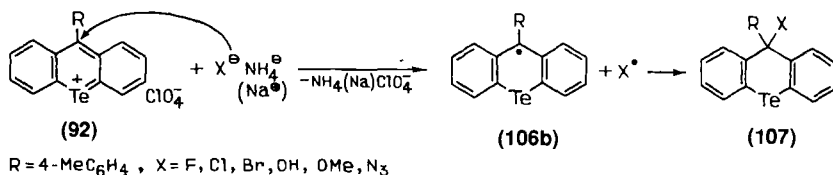


(70MP543), and selenium (74CPB32) analogs. No hyperfine interaction of the unpaired electron with the protons in the 9-phenyl ring of 9-phenyltelluraxanthyl radicals was observed. It was suggested that the phenyl ring in **106** (R = Ph) is turned out of the plane of the heterocycle at a larger angle than those in its oxygen, sulfur, and selenium analogs, in which case the hyperfine splitting due to interaction with the phenyl protons was recorded. In contrast to its 9-phenyl derivative, the parent telluraxanthyl radical **106** (R = H) formed upon reduction of **93** with zinc powder undergoes in solution an irreversible dimerization to give 9,9'-bis(telluraxanthenyl) **102** (88KGS1196).



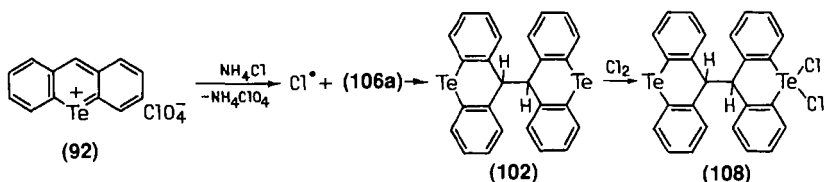
b. *Reactions with Nucleophiles.* Telluraxanthyl radicals serve as the intermediates in reactions of salts of 10-telluroniaanthracene with some nucleophilic reagents (89KGS691). Due to the sharply different kinetic stability of the radicals **106** produced by the telluraxanthylum cation **92** (R = H) and its 9-aryl derivatives **92** (R = aryl), the reactions of these cations with nucleophiles may follow different pathways.

The reactions of 9-(*p*-tolyl)-10-telluroniaanthracene perchlorate with ammonium halogenides, NaOH, MeONa (89KGS691), or NaN<sub>3</sub> in tetrahydrofuran (87KGS279) led to the respective 9-substituted 9-(*p*-tolyl)telluraxanthenes **107** in high yields (64–96%). In some cases, for instance, in the reaction with ammonium chloride, the formation of **106b** was detected by means of ESR spectroscopy.

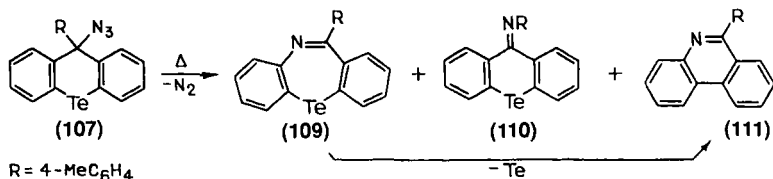




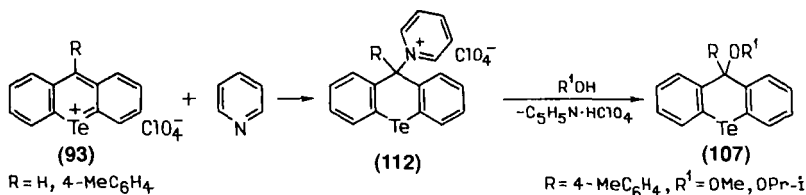
Unlike 9-(*p*-tolyl)-10-telluroniaanthracene perchlorates, the unsubstituted 10-telluroniaanthracene salt **92** ( $R = H$ ), when treated with ammonium chloride, forms 9,9'-bis(telluraxanthenyl)**102** in a mixture with the dichloride **108** (89KGS691).



The thermolysis of 9-(*p*-tolyl)-9-azidotelluraxanthene **107** ( $X = N_3$ ) in refluxing xylene leads to 11-(*p*-tolyl)dibenzo[*b,f*][1,4]tellurazepine **109**, the first representative of the previously unknown tellurazepine heterocyclic system (87KGS279). Along with the tellurazepine **109** obtained in rather low (21%) yield, the arylimine **110** and phenanthridine **111** were also isolated as products of the thermolysis in 32% and 20% yield, respectively.

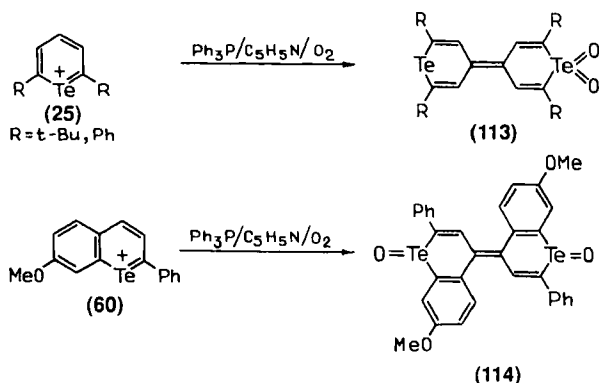


The telluraxanthylum salts **92** readily add pyridine at position 9 to give salts **112** (89KGS691). The pyridinium cation behaves as a good nucleofugal group prone to substitution by alkoxy groups when salts **112** are treated with alcohols.



Under the action of  $Ph_3P$ /pyridine in an atmosphere of oxygen, tellurapyrylium and tellurachromylium salts undergo oxidative dimerization, affording 1,1-dioxo(tellurapyranylidene)tellurapyrans **113** and 1,1'-dioxo(benzo[*b*]pyranilidene)tellurapyrans **114**, the yields of each compound approaching 25% (87JOC2123).

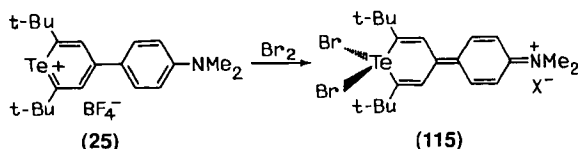
The mechanisms of these reactions remains uncertain. It was suggested



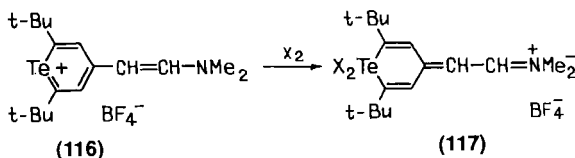
that an important role in the oxidation reaction is played by the triphenylphosphine oxide intermediate. Indeed, whereas compounds **25** and **60** do not convert to dioxides **113** **114** without an excess of oxygen, in the presence of  $\text{Ph}_3\text{PO}$  the reaction occurs under an atmosphere of argon in a degassed solution of acetonitrile in the case of **25** (R = *t*-Bu) or in a melt at 22°C in the case of **60** giving rise to, respectively, **113** (R = *t*-Bu) in 18% yield and **114** in 25% yield. At the same time an attempt at direct oxidation of (tellurapyranilidene)tellurapyran or its benzo derivatives failed. The above reactions are characteristic of tellurium-containing heterocyclic cations. The thia- and selenapyrylium salts under similar conditions afford only (chalcogenapyranilidene)chalcogenapyrans (87JOC2123).

c. *Oxidative Addition Reactions.* Of significant interest is oxidative addition of halogens to tellurapyrylium salts bearing a strong electron-donor, such as a dimethylamino group located in a position conjugated to the tellurium center. The reaction is specific to tellurapyrylium salts and is not found in the chemistry of their sulfur and selenium analogs.

By coupling with bromine under mild conditions 4-(4'-dimethylaminophenyl)tellurapyrylium borotetrafluoride **25** affords 10-Te-4 tellurane **115** in 90–97% yield (86MI2). When bromine is taken in excess, an exchange of anions ( $\text{BF}_4^- \rightarrow \text{Br}_3^-$ ) in **115** takes place. The structure of the compound **115** (X =  $\text{Br}_3^-$ ) has been established by X-ray analysis.

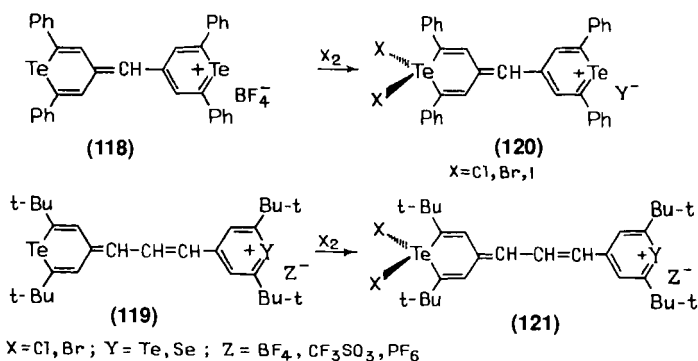


The similar reaction of **116** with bromine or iodine leads to, respectively, dibromide **117** ( $X = \text{Br}$ ) in 67% yield and diiodide **117** ( $X = \text{I}$ ) in 91% yield (86MI2).



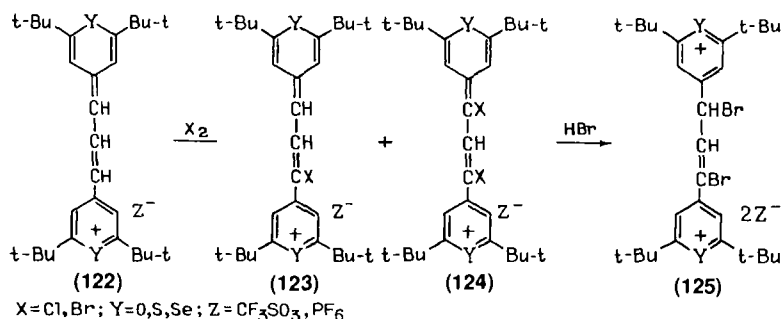
Only one of two tellurium centers on the symmetric mono- and trimethine cyanines **118** and **119** were involved in the oxidative addition reaction.

According to an X-ray study (86MI2) the halogen atoms ( $X = \text{Br}, \text{Cl}$ ) in 10-Te-4 telluranes **120** take the axial positions in the trigonal-bipyramidal coordination polyhedron of the tellurium center.



By contrast, compound **120** ( $X = \text{I}$ ) is better described as a molecular complex of **118** and  $\text{I}_2$ , although all previously studied diorganyltellurium diiodides preferred the structure of 10-Te-4 telluranes with hypervalent  $\text{Te}-\text{I}$  bonds. Owing to the established relationships between the structure of the adducts of diorganylchalcogenides and halogens and differences in the electronegativities of the corresponding interacting centers (69JA5749; 72JA8172; 83CL675), one may conclude that the effective electronegativity of the tellurium donor center in **120** is substantially enhanced when it is incorporated into a cationic species.

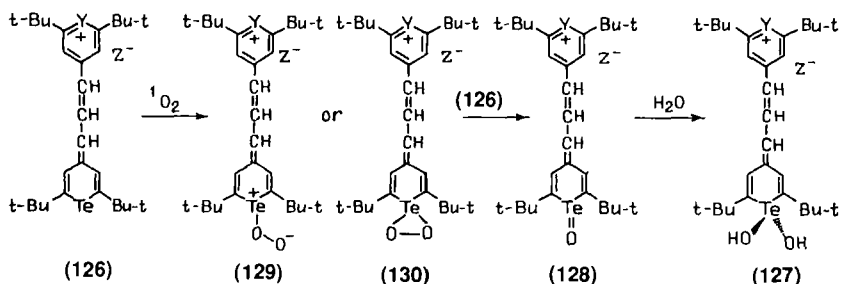
Non-tellurium-containing type-**123** trimethine dyes have been found recently to be susceptible to a reaction with chlorine and bromine (93MI1; 94MI1). In this case, however, the reaction is rather slow and occurs at the trimethine bridges. For the formation of dihalogenides **124**, halogens must be present in at least 2.5-fold excess to the initial trimethine cyanine **122**.



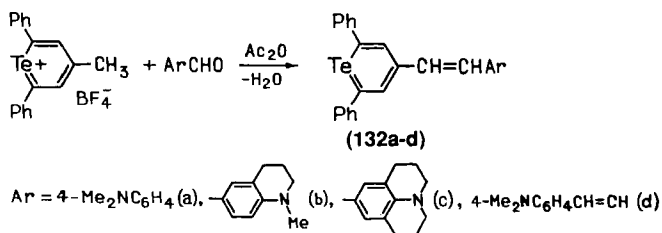
Of special interest are the recently discovered and now thoroughly studied reactions of oxidative addition of hydrogen peroxide or singlet oxygen in the presence of water to trimethine tellurium-containing dyes **126**, leading to dihydroxytelluranes **127** (88JA5920; 90JA3845, 90JA4086; 91MI1). The latter reaction proceeds smoothly under UV irradiation in water-methanol solutions of tellurapyrylium dyes **126**—conditions favoring the formation of singlet oxygen (chalcogenapyrylium dyes serve as effective photosensitizers for singlet-oxygen generation) which oxidizes **126** to telluroxide **128**.

A flash-photolysis study has provided insight into the mechanism of oxidation (90JA3845). The formation of pertelluroxide **129** or telluradioxirane **130** has been proposed as an intermediate step. Then hydration of the telluroxide occurs readily to give dihydroxy derivatives **127**. Such a reaction is common to both dialkyl- and arylalkyltelluroxides (74MI1; 80JOC274; 83MI2). Non-tellurium-containing chalcogenapyrylium cations are not subject to this type of reaction since singlet oxygen attacks their  $\pi$ -conjugated carbon framework instead of the heteroatom (90JA3845).

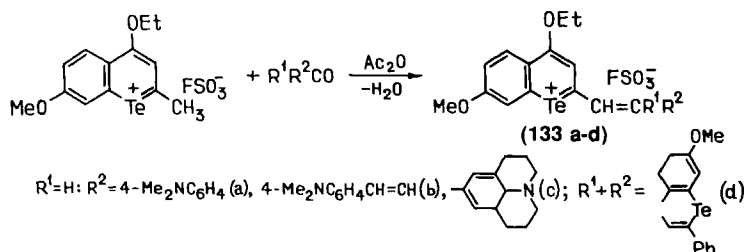
The Te(II)→Te(IV) oxidation reactions of tellurapyrylium dyes **126** are much faster than reactions of the carbon  $\delta$ -backbone. Singlet oxygen reacts with **126** (Y = Se, Te) with a second-order rate of about 10 dm<sup>3</sup>mol<sup>-1</sup>s<sup>-1</sup>. An extremely high rate of oxidation was detected when ozone was used as an oxidant. The large second-order rate constant







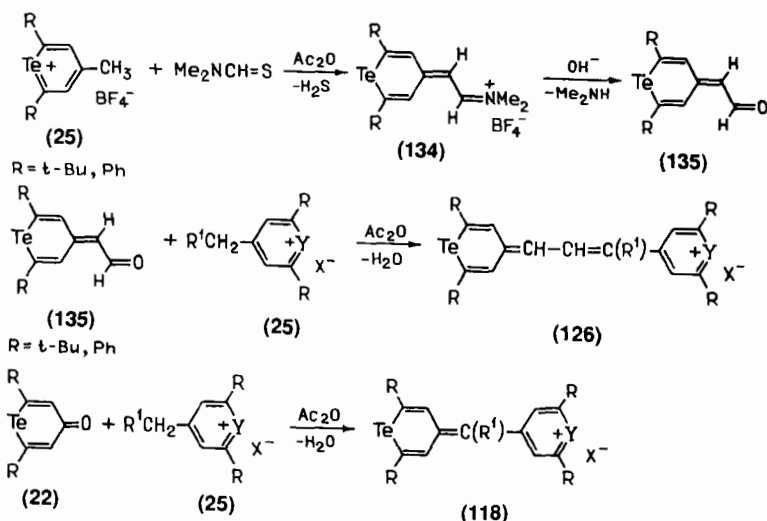
tellurapyrylium salts and 2-methyltellurachromylium salts readily react with aromatic aldehydes and ketones to give the corresponding styryl derivatives. Thus, 4-methyl-2,6-diphenyltellurapyrylium tetrafluoroborate affords **132a-c** in 72–90% yields when refluxed (2–4 minutes) with *p*-dimethylaminobenzaldehyde or its derivatives in acetic anhydride. When *p*-dimethylaminocinnamic aldehyde is used in this condensation, the yield of **132d** is substantially lower (22%) (82JOC5235). The styryl dyes **132a-d** possess long-wave absorption in the range of  $\lambda_{\text{max}}$  from 563 nm for **132a** to 870 for **132d** (82JOC5235).



2-Methyltellurachromylium salts react similarly, although the yields of the styryl derivatives **133a-d** (16–67%) are relatively low. At the same time the tellurachromylium salts react with *p*-dimethylaminobenzaldehydes faster than their oxygen analogs (88MI3).

On reaction of 4-methyltellurapyrylium cations **25** with *N,N*-dimethylthioformamide in acetic anhydride, iminium salts **134** were obtained in almost quantitative yields (82JOC5235; 86MI2; 88MI3). Hydrolysis of **134** leads to (4*H*-tellurapyran-4-ylidene)acetaldehyde **135** which serves as a precursor to the trimethine cyanine dyes **126**. Monomethine dyes of type **118** are obtained by coupling 4*H*-tellurapyrones **22** with tellurapyrylium salts **25** (M = Te) and their analogs in acetic anhydride (82JOC5235; 86MI2; 88MI3).

Reactions of 4-methyltellurapyrylium salts with 1,1,3-trimethoxypropene and 1-chloro-2,6-diformylcyclohex-1-ene were employed for the



preparation, respectively, of tellurium-containing pentamethine **136** and heptamethine cyanine dyes **137** (82JOC5235). Although rather unstable when exposed to light and air, these dyes have an important advantage in that their absorption is markedly shifted to the long wavelengths as compared with the oxygen, sulfur, and selenium analogs.

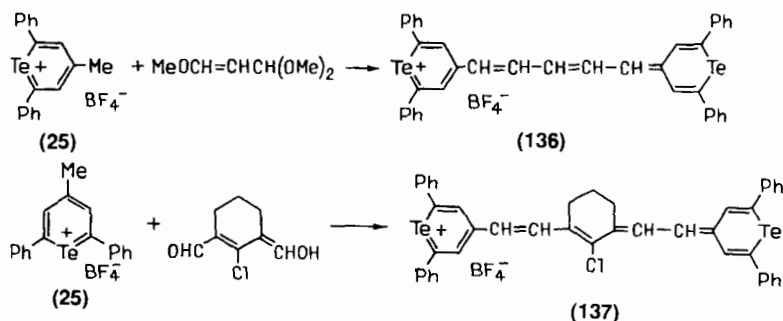


Table VII summarizes the data on longwavelength absorption bands of **138–140** polymethine cyanine dyes (82JOC5235; 88MI3).

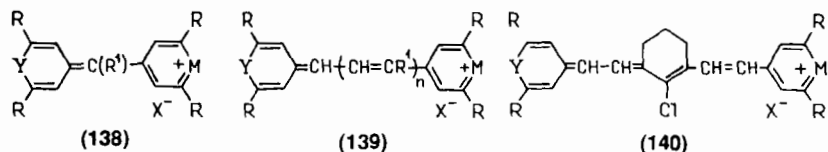
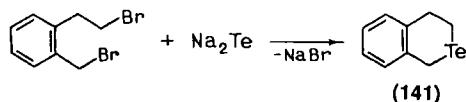


TABLE VII  
LONG-WAVE ABSORPTION OF METHINE AND POLYMETHINE DYES 138-140

Compound type	Y	M	R	R <sup>I</sup>	X <sup>-</sup>	$\lambda_{\max}$ , nm (7)
138	O	O	Ph	H	ClO <sub>4</sub>	545
138	S	S	Ph	H	ClO <sub>4</sub>	622
138	Se	Se	Ph	H	ClO <sub>4</sub>	667
138	Te	Te	Ph	H	BF <sub>4</sub>	759
138	O	Te	Ph	H	BF <sub>4</sub>	650
138	S	Te	Ph	H	ClO <sub>4</sub>	690
138	Se	Te	Ph	H	ClO <sub>4</sub>	722
138	O	Te	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	H	BF <sub>4</sub>	594
138	S	Te	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	H	BF <sub>4</sub>	651
138	Se	Te	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	H	BF <sub>4</sub>	674
138	Te	Te	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	H	BF <sub>4</sub>	715
138	O	Te	Ph	Me	PF <sub>6</sub>	720
138	S	Te	Ph	Me	PF <sub>6</sub>	762
138	Se	Te	Ph	Me	PF <sub>6</sub>	795
138	Te	Te	Ph	Me	PF <sub>6</sub>	834
139, <i>n</i> = 1	O	O	Ph	H	ClO <sub>4</sub>	686
139, <i>n</i> = 1	S	S	Ph	H	ClO <sub>4</sub>	751
139, <i>n</i> = 1	Se	Se	Ph	H	ClO <sub>4</sub>	795
139, <i>n</i> = 1	Te	Te	Ph	H	BF <sub>4</sub>	885
139, <i>n</i> = 1	O	Te	Ph	H	ClO <sub>4</sub>	780
139, <i>n</i> = 1	S	Te	Ph	H	ClO <sub>4</sub>	820
139, <i>n</i> = 1	Se	Te	Ph	H	ClO <sub>4</sub>	843
139, <i>n</i> = 1	Se	Te	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	H	BF <sub>4</sub>	786
139, <i>n</i> = 1	Te	Te	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	H	BF <sub>4</sub>	828
139, <i>n</i> = 1	Se	Te	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	Me	ClO <sub>4</sub>	803
139, <i>n</i> = 1	Te	Te	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	Me	BF <sub>4</sub>	843
139, <i>n</i> = 2	S	S	Ph	H	ClO <sub>4</sub>	879
139, <i>n</i> = 2	Se	Se	Ph	H	ClO <sub>4</sub>	910
139, <i>n</i> = 2	Te	Te	Ph	H	BF <sub>4</sub>	1010
140	S	S	Ph	—	ClO <sub>4</sub>	1017
140	Se	Se	Ph	—	ClO <sub>4</sub>	1050
140	Te	Te	Ph	—	BF <sub>4</sub>	1190

### III. Bicyclic Six-Membered Heterocycles with a Tellurium Atom in Position 2

The known compounds of this type are few. In fact, the only well studied representative is telluraisochromane **141** which was obtained in

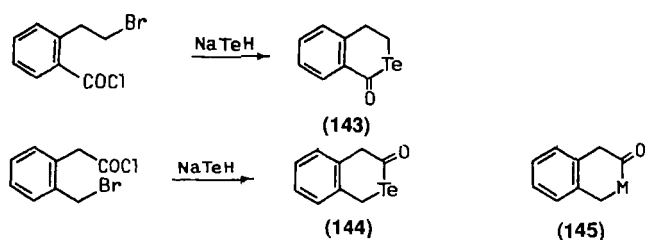




37% yield by the reaction of 2-(2'-bromoethyl)benzyl bromide with sodium telluride [43N(L)749; 45JCS37].

The reactions of **141** are characteristic of the Te(II)-containing heterocycles as featured in Scheme 8.

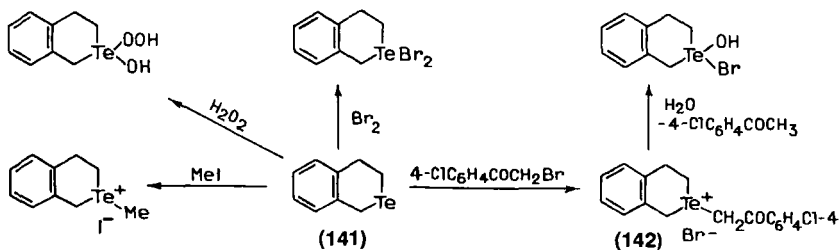
The telluronium salt **142** obtained from telluroisochromane and  $\omega$ -bromo-4-chloroacetophenone upon treatment with silver *o*-bromcamphor-sulfonate produced two diastereomers which were separated by crystallization from ethanol and then converted to their enantiomeric picrates. Racemization due to inversion of their pyramidal configuration at the tricoordinate tellurium center occurs slowly and was accomplished at room temperature over 20 days (45JCS37).



Telluraisochroman-1-one **143** (81JHC343) and telluraisochroman-3-one **144** (83JHC811) have been prepared by treatment of the respective acyl chlorides with sodium hydrotelluride under the conditions of phase-transfer catalysis in the presence of  $\text{Bu}_4\text{N}^+\text{HSO}_4^-$ . The yields are in the range of 50–60%.

A selection of spectral parameters of compounds **145** (83JHC811) is given in Table 8.

A four-step preparative method using 2-ethynylbenzoate as the starting material has been employed to obtain telluraisocoumarin **146** (80JOC3535). Nucleophilic addition of methyltellurolate anion to the triple bond gives rise to a mixture of *Z* and *E* isomers of **147** in a ratio 9 : 1. Hydrolysis and



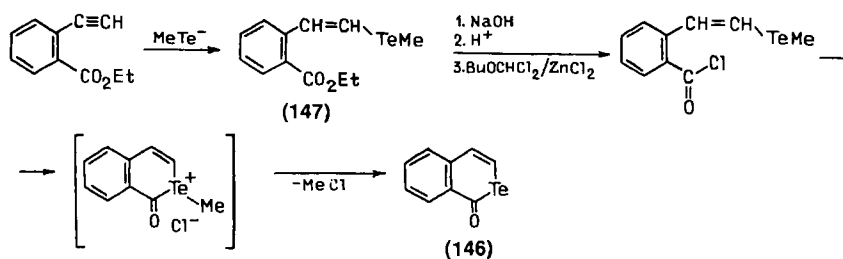
SCHEME 8

TABLE VIII  
IR,  $^1\text{H}$ , AND  $^{13}\text{C}$  NMR SPECTRAL PARAMETERS OF CHALCOGENOISCHROMAN-3-ONES **145**

M	$\nu_{\text{C=O}}, \text{cm}^{-1}$	Chemical Shifts ( $\mu$ , ppm)				
		$\text{H}_1$	$\text{H}_4$	$\text{C=O}$	$\text{C}_1$	$\text{C}_4$
S	1652	4.1	3.7	202.4	34.1	49.2
Se	1665	4.2	3.7	206.4	27.7	52.5
Te	1655	4.3	3.7	209.6	8.5	58.1

subsequent treatment with dichloromethyl butyl ether and cyclization under the action of  $\text{AlCl}_3$  affords **146**.

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## Annulated 1,5-Benzothiazepines

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## I. Introduction

Increasing interest in 1,5-benzodiazepine and 1,5-benzothiazepine systems, with particular reference to their cyclofunctionalization, has stimulated research on these classes of compounds; consequently, a considerable number of papers and patents have appeared in literature. While the condensed 1,5-benzodiazepines have been recently reviewed [93H(36)601, 93H(36)865], no survey dealing with the related 1,5-benzothiazepines has yet been reported. Therefore, this article appears to be the first review on this important group of heteropolycyclic compounds, starting from 1968, when the first synthesis of condensed 1,5-benzothiazepines appeared, to date. This review is divided into two sections depending on whether a monocyclic or bicyclic system is fused onto the thiazepine ring, and both are subdivided into subsections. Derivatives with three-, four-, five-, and six-membered rings fused to different faces of the seven-membered ring are reported in order of increasing size of the fused heterocycle and the number of heteroatoms. The site of fusion is indicated by

numbers and a letter, and the numbering of the heterocyclic systems is that reported by *Chemical Abstracts*. This review will not cover the fusion of heterocyclic rings with the benzene nucleus of the benzothiazepine system. The biological activity of the reported compounds, where tested, is included.

## II. Tricyclic 1,5-Benzothiazepines

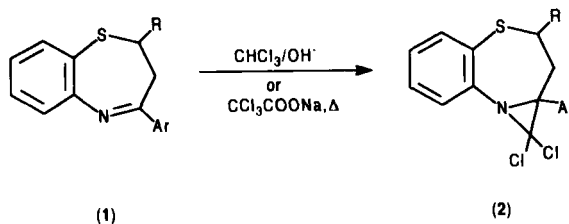
A large number of monoannulated 1,5-benzothiazepines are well known, and a wide variety of synthetic methods for their preparation is available. This section is divided into thirteen subsections, according to the heterocycle fused to the thiazepine nucleus, and each type is subdivided according to the nature of the fusion on the seven-membered ring.

### A. AZIRINO-1,5-BENZOTHAZEPINES

There are three possible azirino-1,5-benzothiazepines. However, those bonded on edges *b* and *c* have not been reported to date, and only one paper concerning the synthesis of azirino[2,1-*d*][1,5]benzothiazepines has appeared.

#### 1. Azirino[2,1-*d*][1,5]benzothiazepines

The reaction of dihydrobenzothiazepines (**1**) with dichlorocarbene, generated *in situ* from chloroform using a phase-transfer catalyst or by thermal decomposition of sodium trichloroacetate, afforded compounds **2** in low yields (18–24%) (Scheme 1). The structure of **2** was postulated on the basis of analytical and spectroscopic data and confirmed by X-ray diffraction (92MI1).



SCHEME 1

## B. AZETO-1,5-BENZOTHIAZEPINES

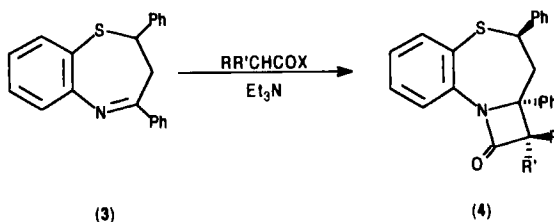
As is the case for azirino-1,5-benzothiazepines, for azeto-1,5-benzothiazepines the only known example concerns the fusion on the *d* edge of the seven-membered ring.

### 1. Azeto[2,1-*d*][1,5]benzothiazepines

The synthesis of  $\beta$ -lactam derivatives of 1,5-benzothiazepines was reported together with the results of NMR investigation on the stereochemistry of the compounds obtained (88CJC279, 88MI1). The reaction of dihydrobenzothiazepine (3) with several acyl halides gave azeto[2,1-*d*][1,5]benzothiazepin-1-one derivatives 4 in 19–86% yields (Scheme 2). The reaction was carried out in the presence of triethylamine and the reactants were refluxed for 1 hour in benzene. The configurational and conformational characteristics of the compounds were deduced by NOE experiments. The preferred conformation of the seven-membered ring is a half-chair and is independent of the substituents present on the four-membered ring. The disposition of the substituents should be governed by steric factors and only in one case ( $R = \text{Me}$ ,  $R' = \text{Br}$ ), were two C-2 epimers isolated.

## C. PYRROLO-1,5-BENZOTHIAZEPINES

As is the case with other five-membered rings condensed to 1,5-benzothiazepines, pyrrolo derivatives have received intensive study and several synthetic routes have appeared. Although it would be possible to obtain several pyrrolo-1,5-benzothiazepines, only two types of fusion have been reported.



SCHEME 2

### 1. Pyrrolo[3,4-*c*][1,5]benzothiazepines

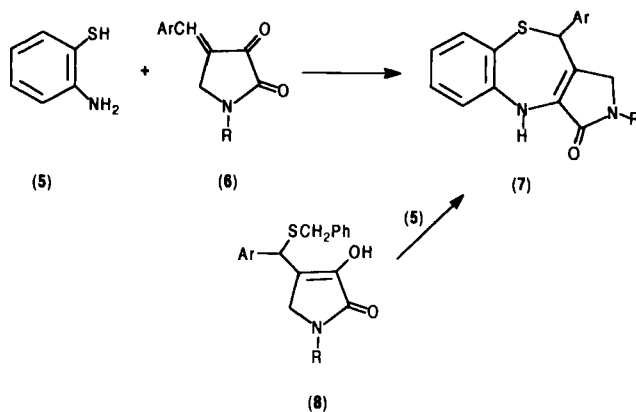
The synthesis of pyrrolo[3,4-*c*][1,5]benzothiazepines was generally carried out by Michael addition of 2-aminothiophenol to  $\alpha,\beta$ -unsaturated ketones and concomitant cyclization. The reaction of 2-aminothiophenol (5) with 4-arylmethylenepyrrolidine-2,3-diones (6) by heating under reflux in ethanol for 1 hour afforded 1,2,4,10-tetrahydro-3*H*-pyrrolo[3,4-*c*][1,5]benzothiazepin-3-ones (7) in good yields [71JCS(C)3875; 93MI1]. Compounds 7 were also synthesized by reacting 6 with toluene- $\alpha$ -thiol and subsequent treatment of products 8 with 5 under the same experimental conditions (Scheme 3) [71JCS(C)3875].

3,3-Dimethyl-2,3,4,10-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,5]benzothiazepin-1-ones (10) were prepared by a reaction between 2-aminothiophenol (5) and 3-arylmethylene-5,5-dimethyltetramic acids (9) in 81–96% yields (Scheme 4) (84YZ1004).

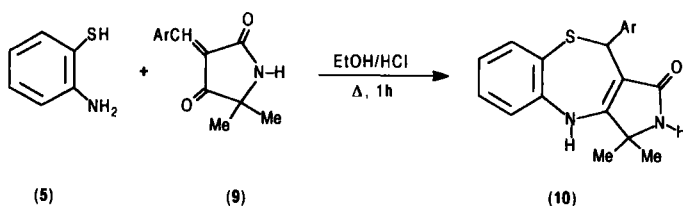
Analogously, 4,10-dihydro-1*H*-pyrrolo[3,4-*c*][1,5]benzothiazepine-1,3 (2*H*)-diones (12) were easily obtained in 47–94% yields by acid-catalyzed cyclocondensation of 4-arylmethylenepyrrolidine-2,3,5-triones (11) with 2-aminothiophenol (5) (Scheme 5) (87S937).

### 2. Pyrrolo[2,1-*d*][1,5]benzothiazepines

Some pyrrolo[2,1-*d*][1,5]benzothiazepine 5,5-dioxides (14) have been synthesized starting from 1-(2-arylmethylsulfonylphenyl)pyrroles (13) through Vilsmeier–Haack formylation and successive base-catalyzed intramolecular cyclization (Scheme 6) (72FES1003; 73FES494; 80FES279).



SCHEME 3

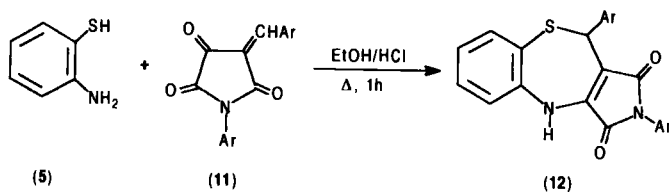


SCHEME 4

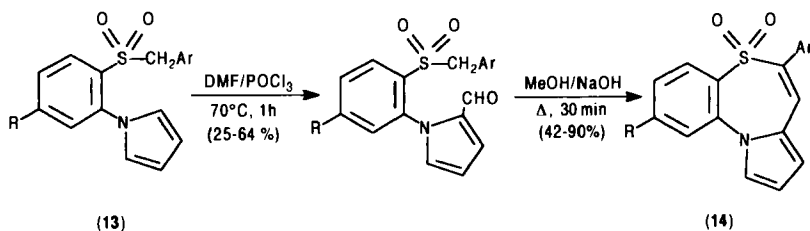
Some derivatives **14** showed marked sedative activity comparable or superior to that exhibited by diazepam (73FES494; 80FES279).

Similarly, the synthesis of 8,9-dihydropyrrolo[2,1-*d*][1,5]benzothiazepine-7,10(6*H*,7*aH*)-dione 5,5-dioxides (**16**) was carried out by cyclizing 1-(2-benzylsulfonylphenyl)pyrrolidin-5-one-2-carboxylates (**15**) in boiling xylene in the presence of potassium (Scheme 7) (72FES1003; 73FES494). 7*a*-Carboxyethyl-8-methyl derivative **16** showed slight sedative activity (73FES494).

The same authors reported various synthetic routes to the pyrrolo[2,1-*d*][1,5]benzothiazepine system (81FES765; 83FES112; 84FES289; 90F545). Compounds **20** were prepared from 1-(2-mercaptophenyl)pyrroles (**18**), which reacted with  $\alpha$ -bromoarylacetaldehyde dimethylacetals in boiling ethanol in the presence of sodium ethylate to give intermediates **17** which, by intramolecular thermal cyclization, gave directly pyrrolo[2,1-*d*][1,5]benzothiazepines (**20**). By the reaction of **18** with  $\alpha$ -bromoarylacetic acids in EtOH/EtONa at room temperature, pyrroles **19** were prepared. By addition of phosphorus pentachloride to a carbon disulfide solution of **19**, the corresponding acyl chlorides were obtained which, upon intramolecular cyclization carried out in boiling dichloromethane with an equimolecular amount of aluminum chloride, afforded pyrrolo[2,1-*d*][1,5]benzothiazepin-7(6*H*)-ones (**22**). As is shown in Scheme 8, ketone **22** was treated with potassium hydride in anhydrous tetrahydrofuran at room temperature, and then with the suitable acyl chloride, to provide esters **23** in 17–100% yields. Furthermore, by reduction with lithium aluminum hy-



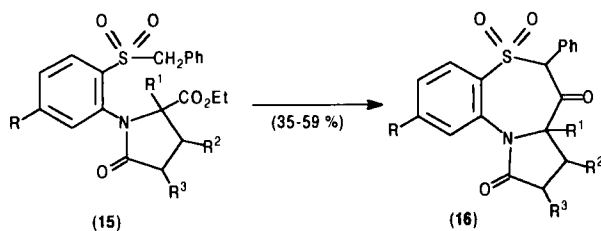
SCHEME 5



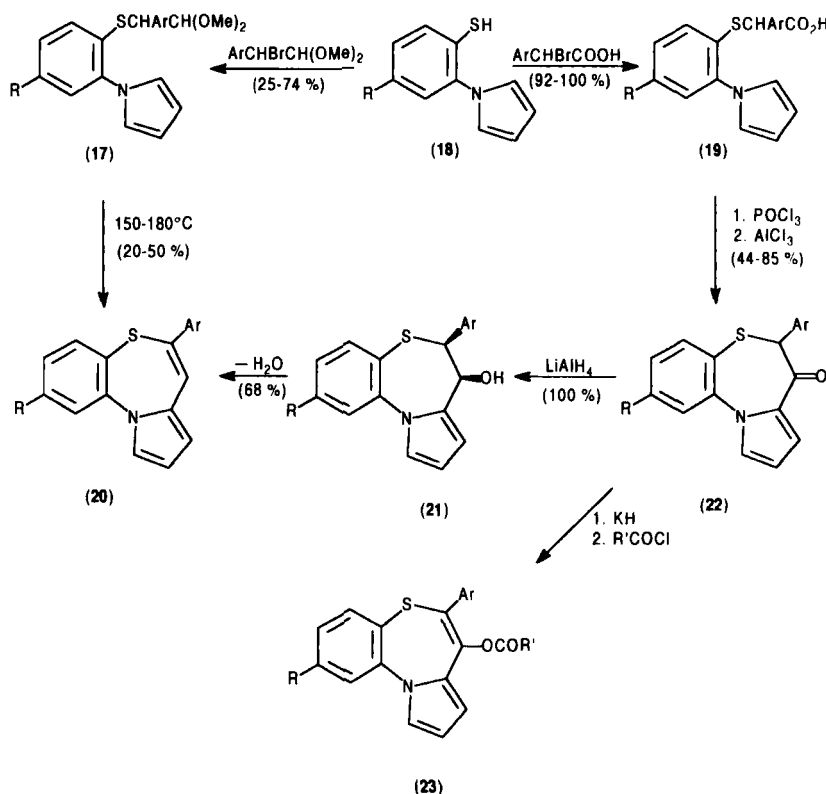
SCHEME 6

dride in anhydrous tetrahydrofuran, ketone **22** yielded *cis*-6,7-dihydro-7-hydroxypyrrolo[2,1-*d*][1,5]benzothiazepines (**21**). The practically stereospecific course of the reaction was established by the conversion of the acetyl derivative of **21** into **20** on treatment with sodium hydride in refluxing dioxane and from  $^1\text{H}$ -NMR spectra. To confirm the structure, **20** was also prepared from **21** by dehydration in dimethyl sulfoxide (Scheme 8). Some of these compounds were tested *in vitro* for inhibition of the specific binding of [ $^3\text{H}$ ]flunitrazepam, [ $^3\text{H}$ ]PK11195, [ $^3\text{H}$ ]muscimol and [ $^3\text{H}$ ]baclofen to central and peripheral benzodiazepine, GABA-A, and GABA-B receptors, respectively. Some compounds—**21** and particularly derivatives **23** and their corresponding sulfonic esters—were active on the peripheral benzodiazepine receptor. Compound **23** (Ar = *p*-MeOC<sub>6</sub>H<sub>4</sub>, R = H, R' = Et) showed an affinity, even though scant, for the central benzodiazepine receptor (90F545).

Pyrrolo[2,1-*d*][1,5]benzothiazepine-6-carboxylic acid (**27**) was obtained via base-catalyzed cyclization of pyrrole-2-carboxaldehydes **26** and **28**, each synthesized by Vilsmeier–Haack formylation of their respective pyrroles **24** and **25**, prepared in turn by condensation of **18**, respectively, with ethyl bromoacetate and chloroacetonitrile in the presence of sodium ethylate at room temperature. When treated with piperidine in refluxing benzene for 48 hours, **26** and **28** afforded ester **29** and nitrile **31** from which, in an alkaline medium, acid **27** could be obtained. Under similar experimental conditions, acid **27** was also formed from amide **30** (Scheme



SCHEME 7



SCHEME 8

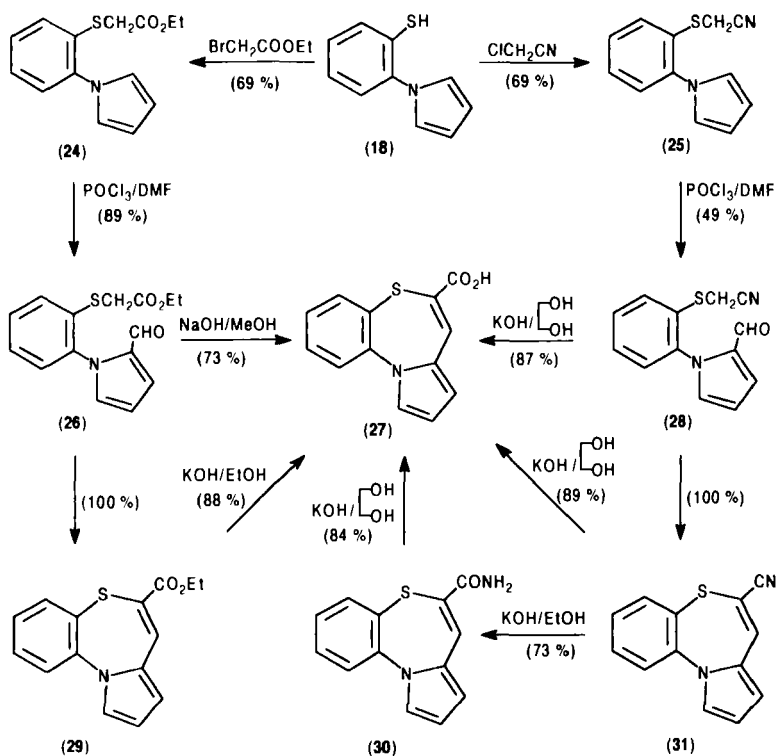
9) (81FES765). Compound **30** showed sedative activity similar to that of diazepam.

#### D. FURO-1,5-BENZOTHAZEPINES

Fusion of a heterocyclic ring having an oxygen atom onto the thiazepine nucleus can occur only at faces *b* and *c*. Three combinations are possible for each type of fusion, but only 3,4-*b* and 3,4-*c* are known.

##### 1. Furo[3,4-*b*][1,5]benzothiazepines

3a,9-Dihydro-1*H*,3*H*-furo[3,4-*b*][1,5]benzothiazepin-1-ones (**33**) were synthesized in good yields (54–92%) by treatment of 2-aminothiophenol (**5**) with butenolides **32** in ethanol in the presence of concentrated hydrochloric



SCHEME 9

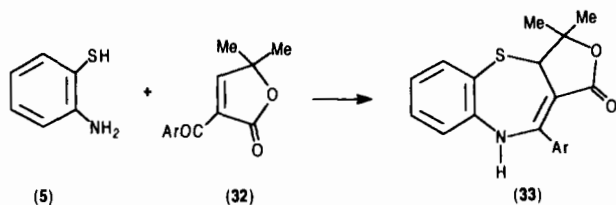
acid, a Michael-type addition reaction, and subsequent intramolecular dehydration (Scheme 10) (89CPB2803).

The same authors recently reported the synthesis of 1*H*,3*H*-furo[3,4-*b*][1,5]benzothiazepin-1-one (35) by cyclizing butanolide 34 in the presence of triethylamine hydrochloride at 170°C and removing the methanol and water formed during the reaction. When the cyclization reaction was performed at about 140°C without removal of methanol and water, compound 35 was obtained in only 9% yield, and the major product was 37 (31%), a methanol adduct to 35. The reduction of the C=N bond of 35 with sodium borohydride and the subsequent spontaneous oxidation gave sulfoxide 36 (92MI1) (Scheme 11).

## 2. Furo[3,4-*c*][1,5]benzothiazepines

4,10-Dihydro-1*H*,3*H*-furo[3,4-*c*][1,5]benzothiazepin-1-ones (39) have been obtained by the heteroannellation reaction between 5 and 3-arylmeth-



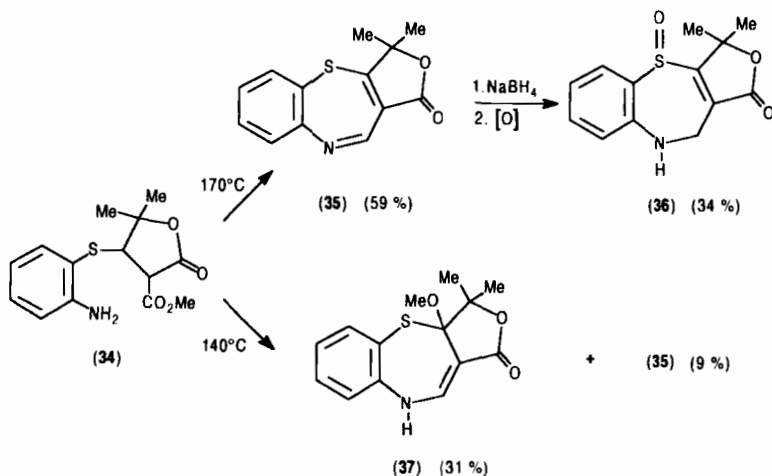


SCHEME 10

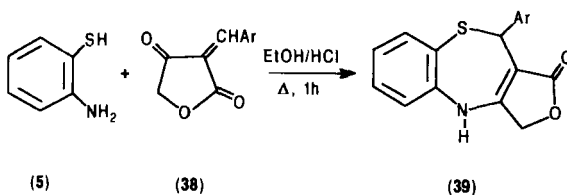
ylenefuran-2,4(3*H*,5*H*)-diones (38) (Scheme 12). While the condensation also occurs in the absence of acid, yields are greatly improved (60–98%) when an equivalent amount of concentrated hydrochloric acid is added (83JOC4367).

### E. THIENO-1,5-BENZOTHAZEPINES

As is the case with furo derivatives, the fusion of a thiophene ring can occur only at edges *b* and *c* of the thiazepine ring; otherwise, a heterocyclic ring with two heteroatoms will be obtained. Much work has appeared on the thienobenzothiazepine system and its neuropharmacological activity since its first synthesis was reported in 1968.



SCHEME 11

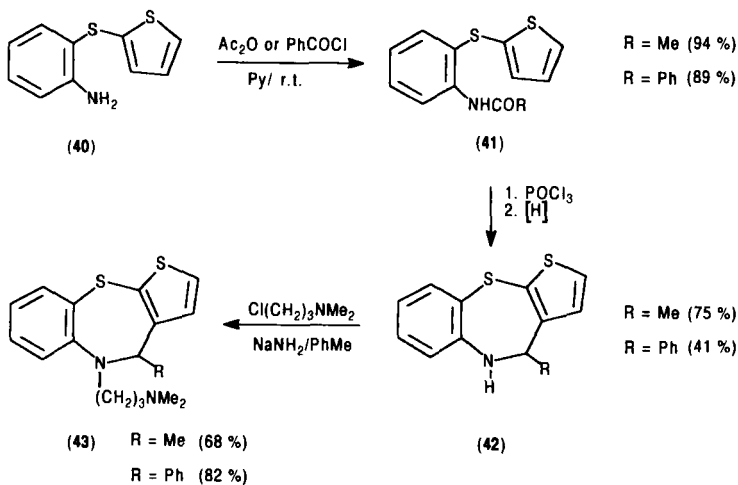


SCHEME 12

### 1. Thieno[2,3-*b*][1,5]benzothiazepines

4,5-Dihydrothieno[2,3-*b*][1,5]benzothiazepines (**42**) were synthesized from 2-(2-thienylthio)aniline (**40**). Compound **40** was acylated by treatment with acetic anhydride or benzoyl chloride to give *N*-acyl derivatives (**41**), which afforded compounds **42** by cyclization with phosphorus oxychloride and subsequent reduction with sodium borohydride or Zn/HCl. *N*-Dimethylaminopropyl derivatives **43** were prepared by reaction with dimethylaminopropyl chloride in the presence of sodium amide (Scheme 13) (67CZP124935; 68CCC1846).

Several patents report the synthesis of thieno[2,3-*b*][1,5]benzothiazepin-4(5*H*)-ones (**45**) as potential antidepressant agents. These derivatives were synthesized from 2-(2-thienylthio)anilines (**40**), which were converted into the corresponding isocyanates **44** by reaction with  $\text{COCl}_2$  and then cyclized by treatment with  $\text{AlCl}_3$ . *N*-Dialkylaminoalkyl derivatives **46** were pre-



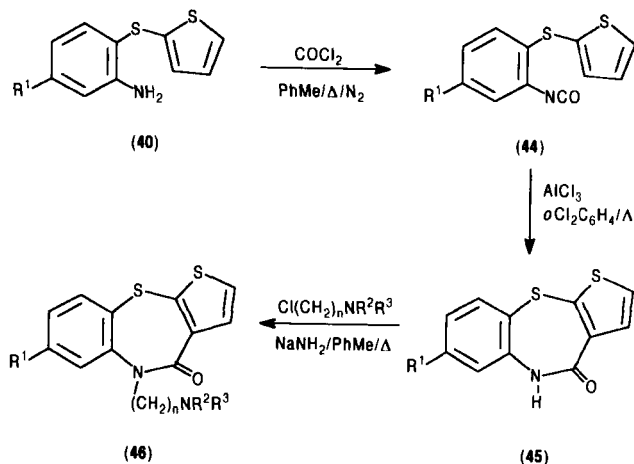
SCHEME 13

pared by reaction of **45** with suitable dialkylaminoalkyl chlorides in an alkaline medium (Scheme 14) [67FRP1505966, 67FRP1505967; 68FRP6292, 68FRP1535533].

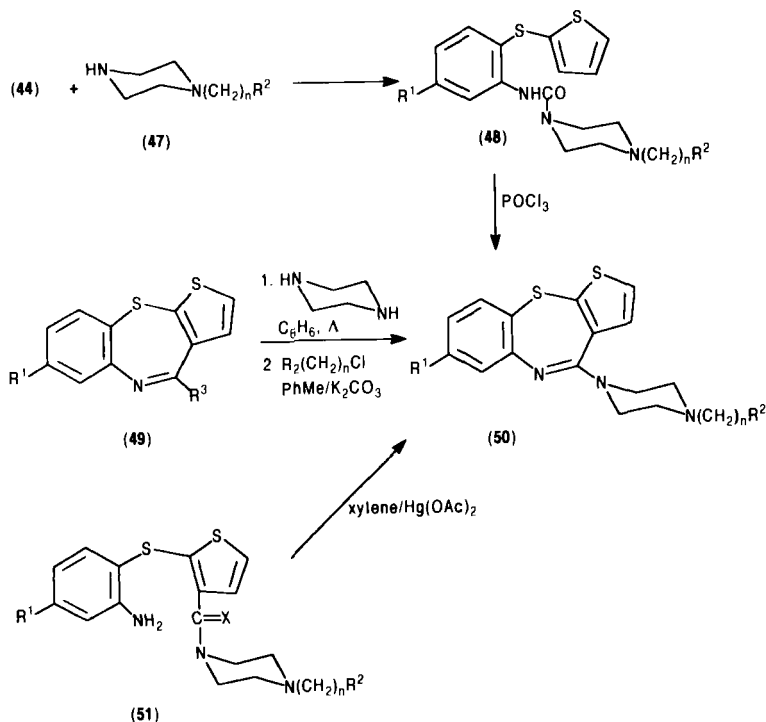
4-Piperazinylthieno[2,3-*b*][1,5]benzothiazepines (**50**) were prepared by various synthetic routes. Isocyanates **44** were refluxed in benzene with piperazines **47** to give 2-(2-thienylthio)-1-piperazinecarboxanilide (**48**), which on treatment with  $\text{POCl}_3$  for 15 hours gave **50** [71GEP(O)2123784]. Derivatives **50**—used as agents for the suppression of spontaneous motility and fighting behavior and for the potentiation of reserpine narcosis—were also prepared by reaction of thieno[2,3-*b*][1,5]benzothiazepines (**49**) ( $\text{R}^3 = \text{Cl}, \text{OH}, \text{SMe}$ ) with piperazine and then with a suitable alkyl chloride [68FRP1535533; 71GEP(O)2039723, 71GEP(O)2123784; 73JAP(K)73/14697, 73SZP531536]. Furthermore, compounds **50** were prepared by the reaction of thieno[2,3-*b*][1,5]benzothiazepin-4(5*H*)-ones (**45**) with *N*-substituted piperazines **47** [73GEP(O)2316438] or by ring closure of (thio)amides **51** (Scheme 15) [73JAP(K)73/52798].

## 2. Thieno[3,2-*b*][1,5]benzothiazepines

Several 10-piperazinylthieno[3,2-*b*][1,5]benzothiazepines (**57**) were synthesized and their neuropharmacological activity evaluated (89MI1; 92AF896). Thieno[3,2-*b*][1,5]benzothiazepin-10(9*H*)-ones (**53**) were prepared by heating compounds **54** for a short time at  $220^\circ\text{C}$  or by cyclizing isocyanates **52** with aluminum chloride [69GEP(O)1811824; 85JHC1345,



SCHEME 14

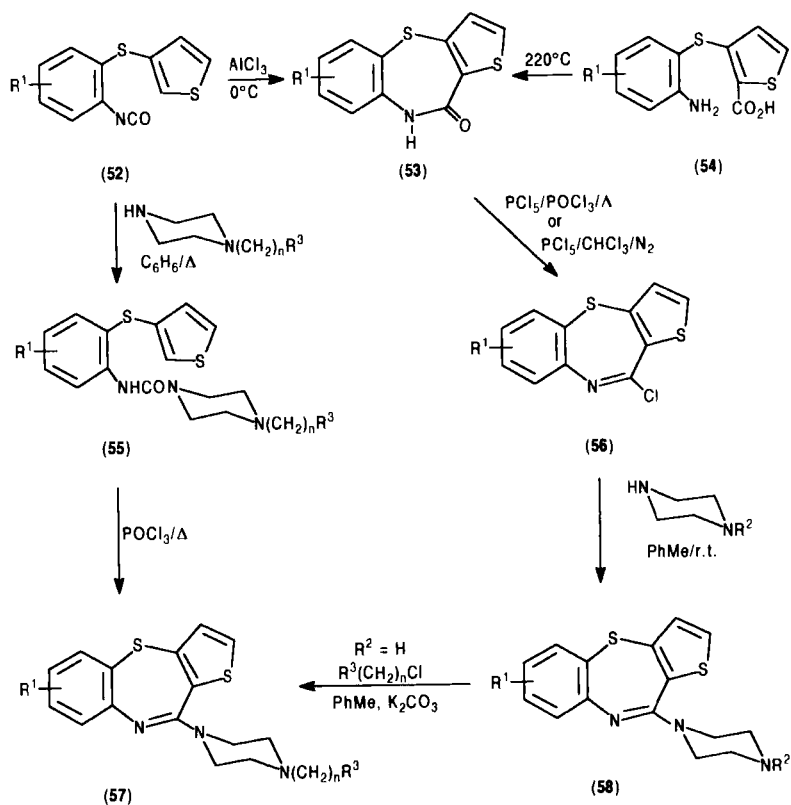


SCHEME 15

85MIP1]. Compounds **53** were converted into the corresponding iminochlorides **56** which, on reaction with various piperazines, gave compounds **58**; the latter ( $\text{R}^2 = \text{H}$ ), following treatment with an alkyl chloride, afforded 10-piperazinyl derivatives **57**, which were also prepared by cyclizing 2-(3-thienylthio)-1-piperazinecarboxanilides (**55**), obtained from **52**, with piperazines (Scheme 16) [71GEP(O)2123784; 73JAP(K)73/14697].

### 3. Thieno[3,4-b][1,5]benzothiazepines

The synthesis of thieno[3,4-b][1,5]benzothiazepin-10(9*H*)-ones (**60**) was carried out by cyclizing mercaptans **59** in the presence of polyphosphoric acid; the reaction afforded compounds **60** and benzothiazoles **61** in approximately equal amounts. Lactams **60** were transformed into 10-piperazinyl derivatives **63** directly on treatment in refluxing toluene with piperazines or through the formation of iminochloride intermediates **62**, which then reacted with an excess of piperazines under the same experimental

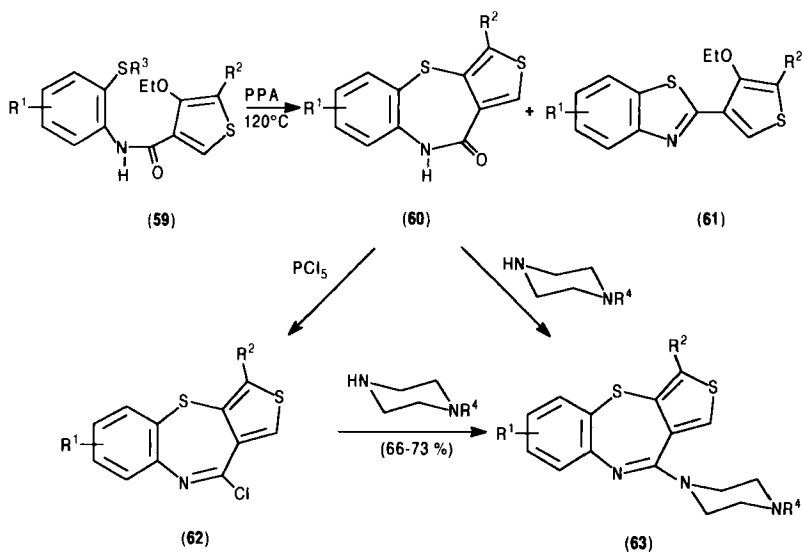


SCHEME 16

conditions (Scheme 17) (79USP4144235, 79USP4157444; 80JOC497; 81JMC154).

#### 4. Thieno[3,4-*c*][1,5]benzothiazepines

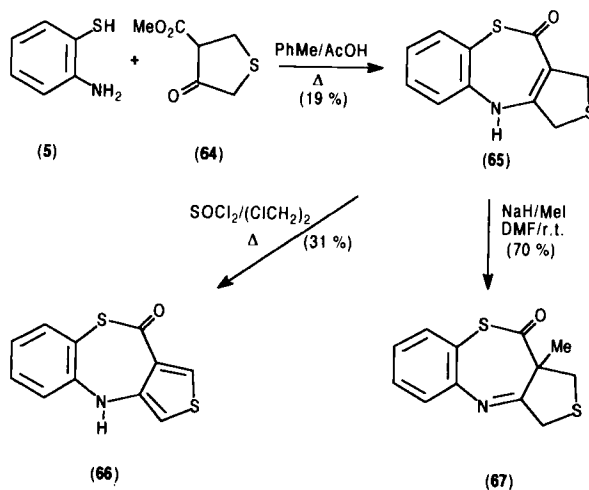
Condensation of **5** with methyl tetrahydro-4-oxothiophene-3-carboxylate (**64**) led to the formation of the ring-closed enamino thiolactone **65**. Chemical transformation of **65** with sodium hydride/methyl iodide gave **67**, whereas 4*H*,10*H*-thieno[3,4-*c*][1,5]benzothiazepin-10-one (**66**) was obtained upon aromatization of the thiophene ring by the action of sulfonyl chloride (Scheme 18) (80JOC497).



SCHEME 17

## F. PYRAZOLO-1,5-BENZOTHAZEPINES

Fusion of a pyrazole ring with a thiazepine nucleus results in three possible isomeric systems, one of which has a nitrogen bridgehead. Whereas this last possibility allows only one fusion, that on the *d* edge,



SCHEME 18

two possible pyrazolobenzothiazepines can be obtained when fusion of the pyrazole nucleus takes place on the *b* or *c* faces of the seven-membered ring. Thus, there are five possible pyrazole-fused derivatives, but only the following three types of pyrazolobenzothiazepines are known.

### 1. *Pyrazolo[3,4-*b*][1,5]benzothiazepines*

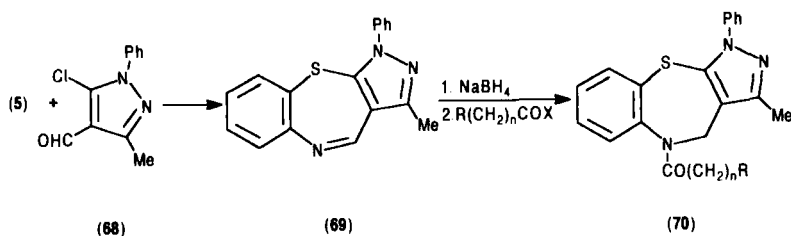
One patent claims the synthesis of 4,5-dihydro-1*H*-pyrazolo[3,4-*b*][1,5]benzothiazepines (**70**) and their hydrochlorides. 2-Aminothiophenol (**5**) was refluxed in toluene with 5-chloro-4-pyrazolecarboxaldehyde (**68**) to give **69**, which was reduced by sodium borohydride and acylated to afford **70** (Scheme 19) [78GEP(O)2707269].

### 2. *Pyrazolo[4,3-*b*][1,5]benzothiazepines*

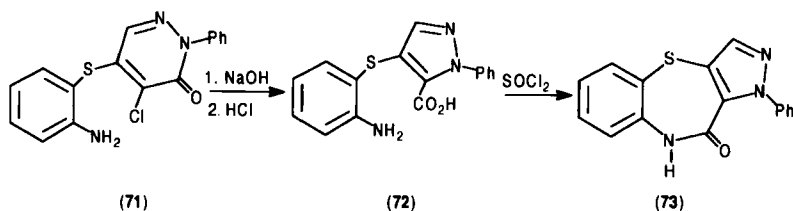
An unusual ring contraction of pyridazinones to pyrazoles is the approach employed for the synthesis of 1-phenylpyrazolo[4,3-*b*][1,5]benzothiazepin-10(9*H*)-one (**73**) [73JAP(K)73/91095; 74CPB229]. Pyrazole-3-carboxylic acid (**72**) was obtained in 70% yield by heating a suspension of pyridazinone **71** in 10% sodium hydroxide at 150°C for several hours, followed by treatment with hydrochloric acid. The *N*-phenyl group is necessary for this type of ring contraction. The cyclization to benzothiazepine **73** in 75% yield was carried out by refluxing **72** with thionyl chloride in boiling chloroform for 1 hour (Scheme 20). When the *N*-methyl group is present, a pyridazinobenzothiazine derivative is obtained.

### 3. *Pyrazolo[3,4-*c*][1,5]benzothiazepines*

The Ulmann reaction of 4-bromo-3-(2-aminophenyl)thiomethyl-3-pyrazolin-5-ones (**74**) in a nonpolar solvent such as xylene and in the presence of a small amount of pyridine afforded 1,2,4,10-tetrahydro-3*H*-pyrazolo[3,4-*c*][1,5]benzothiazepin-3-ones (**75**). However, when the same reaction was



SCHEME 19



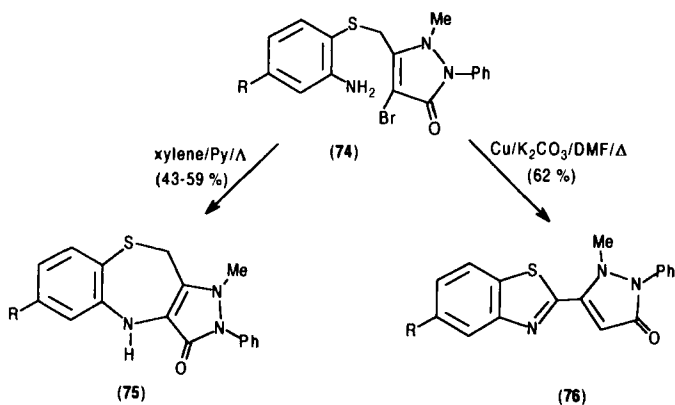
SCHEME 20

carried out in an aprotic dipolar solvent such as dimethylformamide (DMF) in the presence of anhydrous K<sub>2</sub>CO<sub>3</sub> and copper powder, the cyclization predominantly occurred at the bridging methylene group at the 3-position of the pyrazolinone, rather than at the 4-position, to give benzothiazole **76** (Scheme 21) [70CPB2058; 73YZ207].

The attempted allylic bromination of **75** (R = H) with *N*-bromosuccinimide (NBS) in chloroform gave the insoluble 7-bromo derivative **77**, which on reaction with chloroacetyl chloride and subsequent treatment with 40% dimethylamine gave soluble 4-(*N,N*-dimethylglycyl) derivative **78** in 88% yield (Scheme 22) (75CPB1646). The structure of **78** was confirmed by NMR analysis.

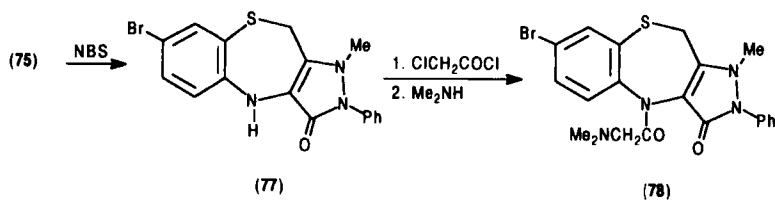
### G. IMIDAZO-1,5-BENZOTHAZEPINES

Only the imidazo[2,1-*d*][1,5]benzothiazepine system belonging to this class has been reported.



SCHEME 21





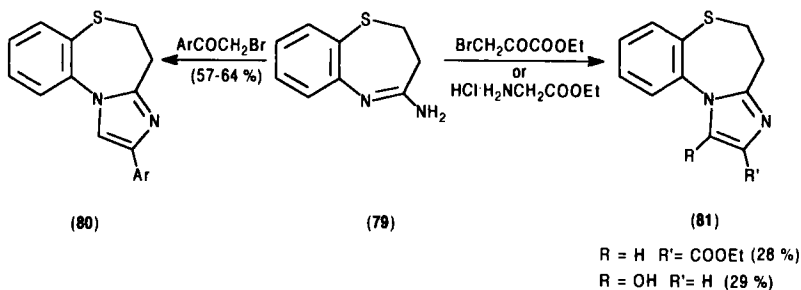
SCHEME 22

### 1. Imidazo[2,1-*d*][1,5]benzothiazepines

A convenient method for the synthesis of imidazo[2,1-*d*][1,5]benzothiazepines is based on the reactivity of 1,5-benzothiazepines incorporating a cyclic amidine functionality. Imidazo[2,1-*d*][1,5]benzothiazepines (**80**) were obtained by treatment of 4-amino-2,3-dihydro-1,5-benzothiazepine (**79**) with phenacyl bromide in ethanol containing sodium bicarbonate. The initial displacement of the bromine atom in phenacyl bromide by the ring nitrogen atom of **79** leads to the resonance-stabilized amidinium ion intermediate. Further loss of hydrogen bromide and water furnishes heterocycle **80** (85JHC1117). The structure of these derivatives was fully characterized by high-resolution  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra. Similarly, imidazo[2,1-*d*][1,5]benzothiazepines (**81**) were synthesized by reaction of **79** with ethyl bromopyruvate in refluxing ethanol or ethyl glycinate hydrochloride in DMF (Scheme 23) (92M1023).

## H. THIAZOLO-1,5-BENZOTHAZEPINES

To date, only the fusion of the thiazole ring to the 1,5-benzothiazepine system involving the *d* face of the seven-membered ring has been reported.



SCHEME 23

### 1. *Thiazolo*[2,3-*d*][1,5]*benzothiazepines*

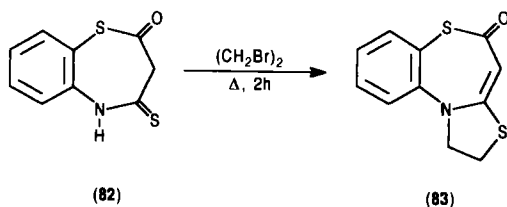
The only known example of thiazolo-1,5-benzothiazepines is 1,2-dihydro-5*H*-thiazolo[2,3-*d*][1,5]benzothiazepin-5-one (**83**), obtained in very low yield (3%) by cyclization of 4-thione derivative **82** with 1,2-dibromoethane in ethanol containing sodium acetate (Scheme 24) (80CB2314).

## I. TRIAZOLO-1,5-BENZOTHAZEPINES

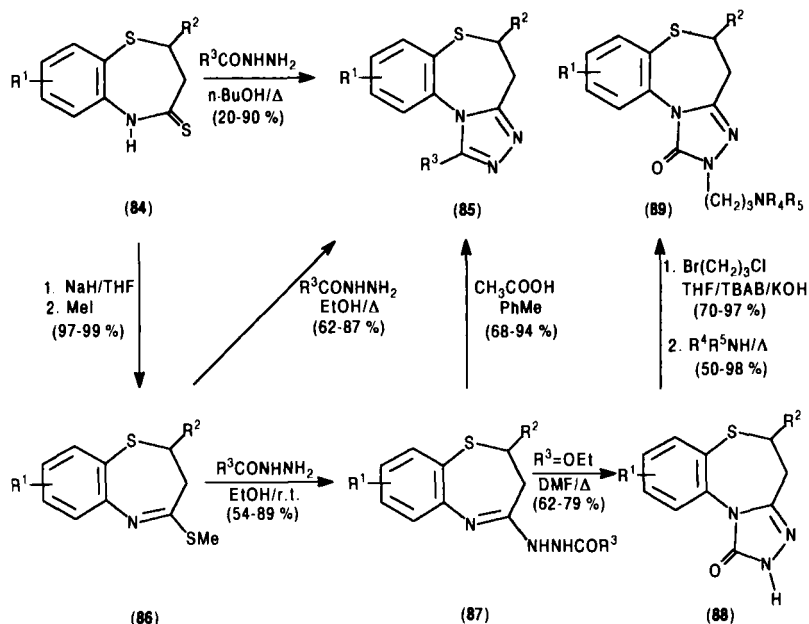
The presence of two or three adjacent nitrogen atoms distinguishes 1,2,4- from 1,2,3-triazoles. These systems could be fused with the thiazepine ring on the *b*, *c*, and *d* edges, but only the fusion of 1,2,4-triazoles on face *d* of the seven-membered ring is known.

### 1. *[1,2,4]Triazolo*[3,4-*d*][1,5]*benzothiazepines*

4,5-Dihydro[1,2,4]triazolo[3,4-*d*][1,5]benzothiazepines (**85**) have been synthesized by cyclization of 1,5-benzothiazepine-4(5*H*)-thiones (**84**) with acyl hydrazides (87FES575). Alternatively, benzothiazepines **84** were activated by conversion into methylthioethers **86**, which, by reacting with carbohydrazides, afforded triazolobenzothiazepines **85**. Under mild reaction conditions, some intermediate *N*-substituted hydrazides **87** were isolated and subsequently cyclized to **85** or 2*H*-4,5-dihydro[1,2,4]triazolo[3,4-*d*][1,5]benzothiazepin-1-ones (**88**). These latter, by phase-transfer catalysis (PTC) alkylation and reaction with the appropriate amine, gave compounds **89** (Scheme 25) (88JHC1151; 89MI2; 92AP569; 93F665). Some compounds **85** were tested for their central nervous system (CNS) activity and effects comparable with that of diazepam were observed (87FES575). Several compounds **89** showed sedative activity without compromising motor coordination, suggesting the lack of hypnotic effects. Compounds



SCHEME 24

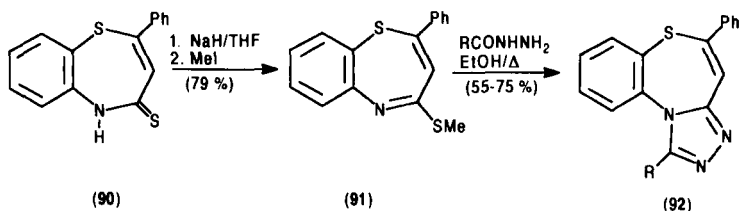


SCHEME 25

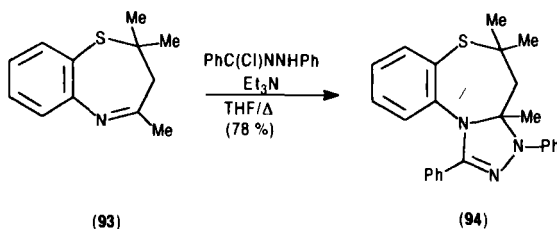
**88** and **89** were also tested *in vitro* for their antimicrobial activity, but none of them showed marked activity (92AP569).

The same authors extended the synthesis to [1,2,4]triazolo[3,4-*d*][1,5]benzothiazepines (**92**), which contain a double bond at the 4,5-position (93F665). 1,5-Benzothiazepine-4(5*H*)-thione (**90**) was converted in two steps into **92**, through the intermediate methylthioether **91** (Scheme 26).

3,3*a*,4,5-Tetrahydro[1,2,4]triazolo[3,4-*d*][1,5]benzothiazepine (**94**) was prepared by 1,3-dipolar cycloaddition of benzonitrile *N*-phenylimine (generated *in situ* from *N*-phenylbenzohydrazonic acid chloride and triethylamine) to 1,5-benzothiazepine (**93**) as dipolarophile (Scheme 27) [88H(27)1461].



SCHEME 26

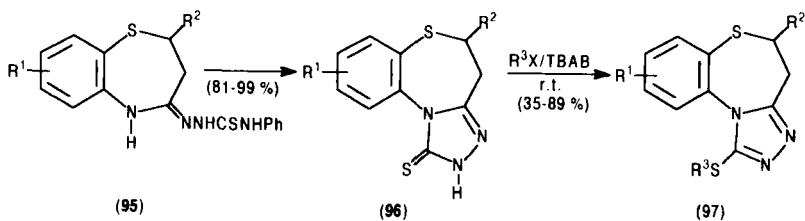


SCHEME 27

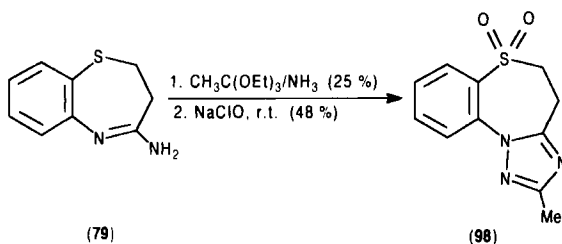
Phenylthiosemicarbazones cyclize easily to triazolo derivatives when heated alone or refluxed in high-boiling solvents. Phenylthiosemicarbazones **95** were refluxed in DMF and cyclized into 4,5-dihydro[1,2,4]triazolo[3,4-*d*][1,5]benzothiazepine-1(2*H*)-thiones (**96**), which can exist either in the thioamidic or in the iminothiolic form. Infrared spectra showed that the thioamidic form seems to be preferred. By PTC alkylation of **96** with methyl iodide, ethyl chloroformate, or chloroacetic acid, the corresponding *S*-substituted derivatives **97** were obtained (Scheme 28) (91M11). Many of the compounds were cytotoxic and hence not screened further; others were tested as antibacterial, antimycotic, and antiviral agents, but no appreciable activity was observed.

## 2. [1,2,4]Triazolo[5,1-*d*][1,5]benzothiazepines

By the reaction of 4-amino-2,3-dihydro-1,5-benzothiazepine (**79**) with triethyl orthoacetate at 150°C followed by treatment with ammonia at room temperature, an acetamidine intermediate was obtained which, by oxidative cyclization with sodium hypochlorite, was converted to 4,5-dihydro[1,2,4]triazolo[5,1-*d*][1,5]benzothiazepine 6,6-dioxide (**98**) (Scheme 29) (92M1023).



SCHEME 28



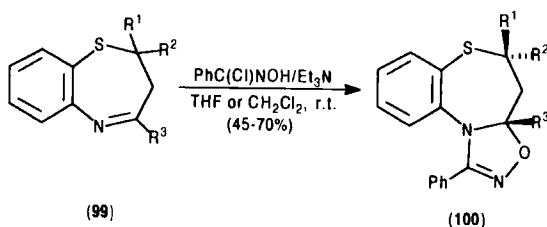
SCHEME 29

### J. OXADIAZOLO-1,5-BENZOTHAZEPINES

Among the possible oxadiazolo-1,5-benzothiazepines, only derivatives containing a 1,2,4-oxadiazole nucleus fused on the *d* edge of the 1,5-benzothiazepine system are reported.

#### 1. [1,2,4]Oxadiazolo[5,4-*d*][1,5]benzothiazepines

[1,2,4]Oxadiazolo[5,4-*d*][1,5]benzothiazepines (**100**) were prepared by 1,3-dipolar cycloaddition of benzonitrile oxide, generated *in situ* from benzohydroxamoyl chloride in the presence of triethylamine, to 1,5-benzothiazepines **99** (Scheme 30) [88H(27)1461; 92M12; 94H(38)2289]. The stereochemistry of the cycloadducts was obtained from NOE measurements and NMR coupling constants, which showed that the seven-membered ring adopts a twisted-boat conformation with the  $R^2$  substituent at C-5 in a quasi-equatorial position and the 3a-substituent in a near-axial one [94H(38)2289]. The anticonvulsant activity of the synthesized compounds has also been investigated (94UP1).



SCHEME 30

## K. TETRAZOLO-1,5-BENZOTHAZEPINES

The examples reported for this system obviously concern the only possible fusion of a tetrazole nucleus on the *d* edge of the 1,5-thiazepine ring with a nitrogen bridgehead.

1. *Tetrazolo[5,1-d][1,5]benzothiazepines*

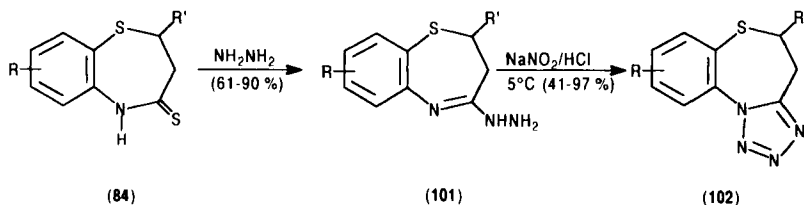
4,5-Dihydro-tetrazolo[5,1-*d*][1,5]benzothiazepines (**102**) were synthesized by nitrous acid treatment of 2,3-dihydro-1,5-benzothiazepin-4-ylhydrazines (**101**), which were prepared from 2,3-dihydro-1,5-benzothiazepine-4(5*H*)-thiones (**84**) by reaction with hydrazine hydrate in tetrahydrofuran (THF) (Scheme 31) (88JHC1399; 89MI2; 93F665). The ability of compounds **103** to displace specific [<sup>3</sup>H]flunitrazepam binding was studied. Only compounds with a chlorine atom at the 9-position were able to interact with [<sup>3</sup>H]flunitrazepam binding sites (93F665).

## L. PYRIDO-1,5-BENZOTHAZEPINES

Syntheses of four different condensed pyrido-1,5-benzothiazepine systems are described in the literature. Several publications concerning pyrido[2,3-*b*][1,5]benzothiazepines are known, but only one synthetic approach was reported for each of the other systems investigated.

1. *Pyrido[2,3-b][1,5]benzothiazepines*

5,6-Dihydropyrido[2,3-*b*][1,5]benzothiazepin-5(6*H*)-ones (**104**) were obtained by cyclocondensation of **5** and 2-chloronicotinic acid (**103**); the reaction of compounds **104** with phosphorus oxychloride and phosphorus pentachloride afforded the corresponding iminochlorides which were refluxed in toluene with piperazines and triethylamine to give compounds **105**. These products showed antihistaminic, orexigenic, and antianaphy-

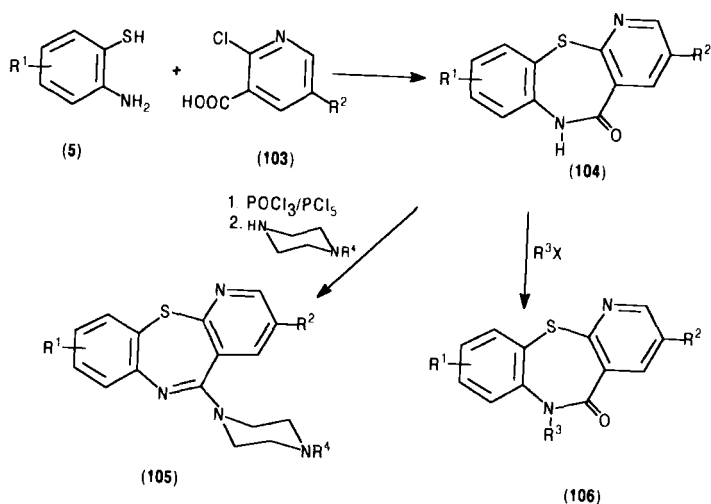


SCHEME 31

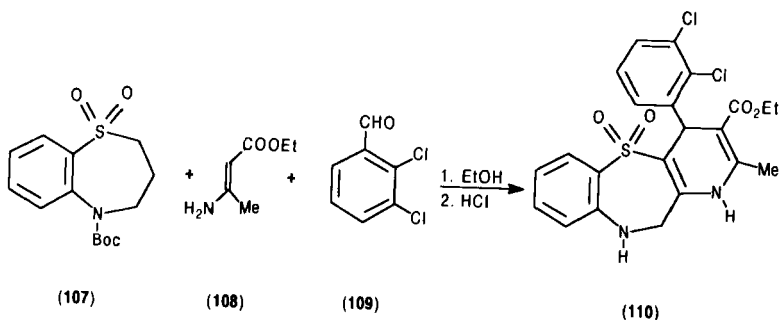
lactic activity [78GEP(O)2815088; 79USP4163785; 83FRP2511683, 83FRP2511684]. When compounds **104** were made to react with alkyl halides in DMF containing sodium hydride, the corresponding *N*-alkyl derivatives **106** were obtained. These latter were evaluated as HIV-1 reverse transcriptase inhibitors (Scheme 32) (91CP2024071, 91EUP415303). The X-ray structure analysis of 5-(4-methyl-1-piperazinyl) derivative **105** ( $R^1 = R^2 = H$ ) has been reported (88CSC319). The thiazepine ring is in a boat conformation while the piperazine ring is in a normal chair conformation. The dihedral angle between the two aromatic rings is  $111^\circ$ . The cohesion of the crystal is the result of van der Waals interactions. In a recent paper (94JMC519), the ability of this compound to interact with dopaminergic, serotonergic, and muscarinic receptors was evaluated in comparison with analogous tricyclic compounds.

## 2. *Pyrido[3,2-b][1,5]benzothiazepines*

1,4,10,11-Tetrahydropyrido[3,2-*b*][1,5]benzothiazepine 5,5-dioxide (**110**) was prepared by a one-pot reaction of benzothiazepine **107** with ethyl 3-aminocrotonate (**108**) and 2,3-dichlorobenzaldehyde (**109**) in boiling ethanol and subsequent deprotection with hydrochloric acid in ethyl acetate (Scheme 33) (91EUP462696). Compound **110** proved to be a potent calcium-channel antagonist.



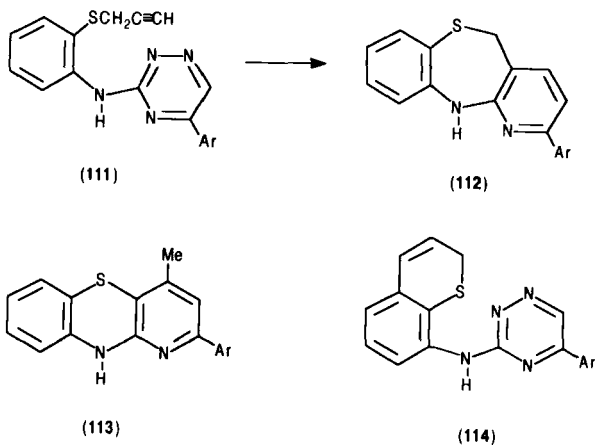
SCHEME 32



SCHEME 33

### 3. *Pyrido[3,2-c][1,5]benzothiazepines*

Intramolecular Diels–Alder reactions of 1,2,4-triazines provide convenient access to condensed pyridine heterocycles. On this basis, thermolysis of propynylthiophenylamino-1,2,4-triazines (**111**) in refluxing bromobenzene over a period of 2–5 days afforded 5,11-dihydropyrido[3,2-*c*][1,5]benzothiazepines (**112**), but in yields that were consistently less than 5% (89JOC1456). The major reaction products were pyridobenzothiazines **113** and benzothiopyranes **114**; the formation of these products, involving a six-membered transition state, is preferred to the formation of the Diels–Alder product **112**, which proceeds through an entropically less favorable seven-membered transition state (Scheme 34).



SCHEME 34



#### 4. *Pyrido[2,1-d][1,5]benzothiazepines*

The synthesis of 7,9-dihydro-6*H*-pyrido[2,1-*d*][1,5]benzothiazepines (**115**) was carried out by reaction of **93** with acetone or 2-butanone in the presence of *p*-toluenesulfonic acid. The reaction also afforded compounds **116** and **117**, which were detected by GC/MS analysis and not isolated (Scheme 35) (89LA601).

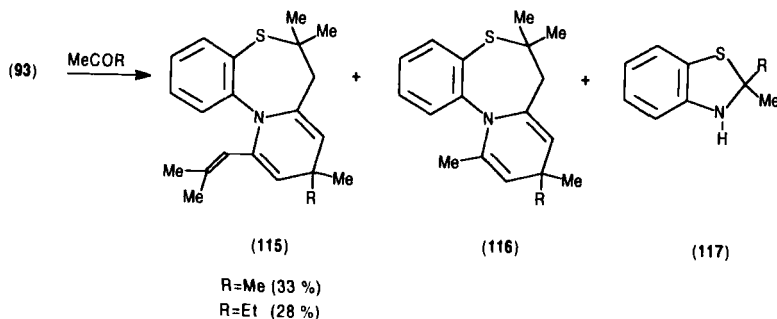
### M. PYRIMIDO-1,5-BENZOTHAZEPINES

Although the first synthesis was reported over twenty years ago, pyrimido[4,5-*b*]- and [5,4-*c*][1,5]benzothiazepines are the only examples of pyrimidobenzothiazepine systems investigated to date.

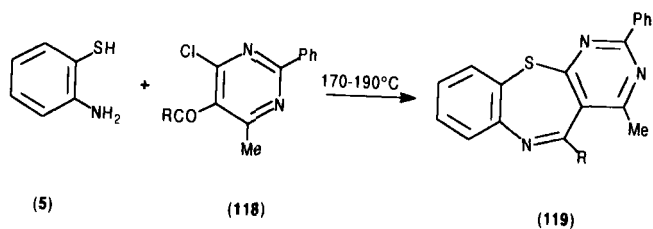
#### 1. *Pyrimido[4,5-b][1,5]benzothiazepines*

Pyrimido[4,5-*b*][1,5]benzothiazepines (**119**) were prepared by reaction of 2-aminothiophenol (**5**) with 4-chloro-5-acylpyrimidines (**118**) in almost theoretical yields (Scheme 36) (73CB3524). The UV, IR, and NMR spectra of this ring system are described.

An intramolecular Mannich-type cyclization of 1,3-dimethyl-6-(2-aminophenylthio)uracil (**120**) has been utilized for the synthesis of 5,6-dihydropyrimido[4,5-*b*][1,5]benzothiazepine-2,4(1*H*,3*H*)-diones (**121**); this synthesis was realized by reaction of **120** with an excess of formaldehyde, benzaldehyde, or *p*-nitro- or *p*-methoxybenzaldehyde in chloroform in the presence of a catalytic amount of *p*-toluenesulfonic acid under reflux for 4–10 hours. The thiazepine cyclization using aliphatic aldehydes other than formaldehyde did not give satisfactory results. In these cases the reaction resulted in the formation of a dimeric product that probably



SCHEME 35

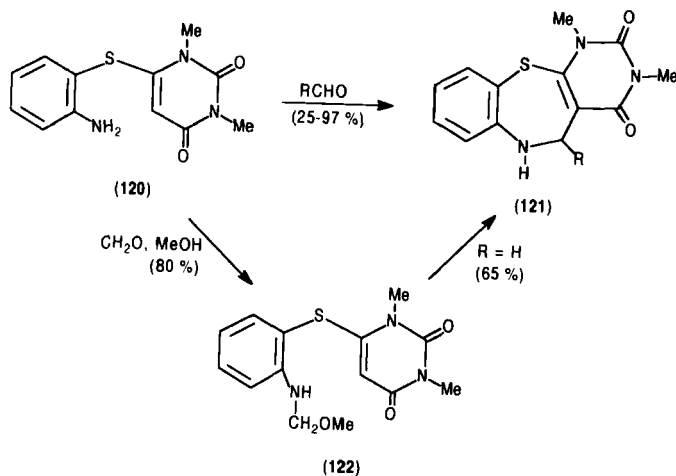


SCHEME 36

arises from the reaction of an intermediate Schiff base with its tautomeric enamine. When the reaction was achieved from **120** and *p*-nitrobenzaldehyde in methanol in the presence of *p*-toluenesulfonic acid at room temperature for 1 hour, a Schiff base intermediate was isolated, which was converted into thiazepine **121** by further heating in chloroform containing *p*-toluenesulfonic acid. When **120** was made to react with formaldehyde in methanol at room temperature, methoxymethylamino derivative **122** was obtained, which led, by treatment with *p*-toluenesulfonic acid, to the formation of **121** ( $\text{R} = \text{H}$ ). The *N*-methyl derivative of **121** was easily obtained in 60% yield with methyl iodide in DMF containing potassium carbonate (Scheme 37) (77S177).

## 2. Pyrimido[5,4-*c*][1,5]benzothiazepines

A convenient preparative method for 5,11-dihydropyrimido[5,4-*c*][1,5]benzothiazepine-2,4(1*H*,3*H*)-diones (**124**) was achieved by the com-



SCHEME 37

bination of the Smiles rearrangement of *N*-acetyl derivative **123** and subsequent Mannich-type acid-catalyzed cyclization. Thus **123** was treated with methanolic sodium hydroxide in the presence of formaldehyde and, without isolation of the intermediate, the reaction mixture was acidified to give the thiazepine **124**. Methylation of **124** with methyl iodide in DMF in the presence of potassium carbonate gave the *C*-Me derivative (**125**) (Scheme 38) (79MI1; 80T2097).

Compounds **128** were prepared in high yields either by thermal [1,2]-rearrangement of sulfonium ylides **126** to intermediates **127** which were then converted into the thiazepine derivatives (**128**) by ring expansion on photolysis in methanol, or directly from the ylides **126** by ultraviolet irradiation, which causes a photo[1,2]rearrangement followed by ring expansion (Scheme 39) (77CPB292).

### III. Tetracyclic 1,5-Benzothiazepines

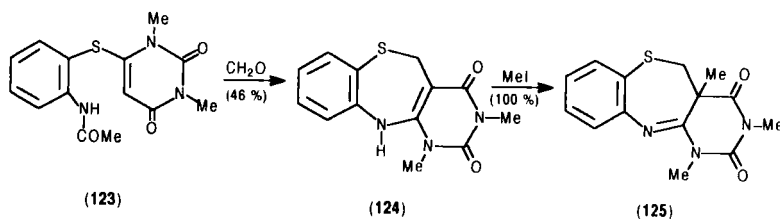
A number of papers have been published on the chemistry and biological activity of 1,5-benzothiazepines containing an additional bicyclic system fused to different positions of the seven-membered ring. Tetracyclic indolo-, benzofuro-, pyrazolopyrido-, quino-, benzopyrano-, benzothio-pyrano-, quinazolino-, and quinoxalino-1,5-benzothiazepines are known.

#### A. INDOLO-1,5-BENZOTHAZEPINES

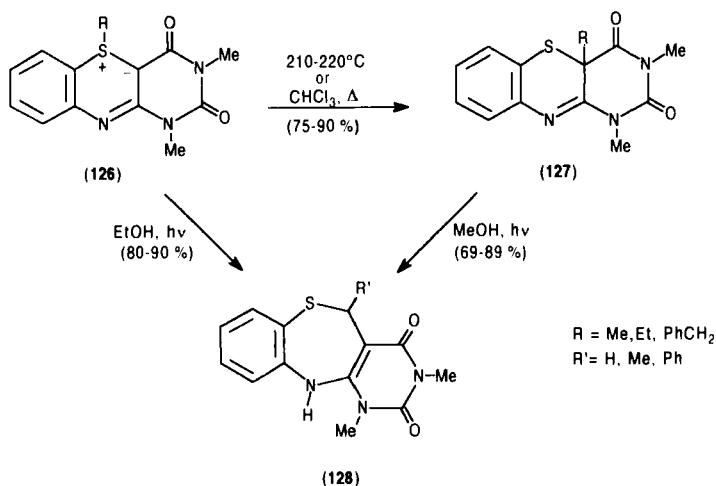
Two examples of synthetic approaches to indolo-1,5-benzothiazepines have been reported along with investigations of their biological activity.

##### 1. *Indolo[2,3-b][1,5]benzothiazepines*

Indolo[2,3-*b*][1,5]benzothiazepines (**130** and **132**) were prepared by Fisher indolization of phenylhydrazone derivatives **129** and **131**, respec-

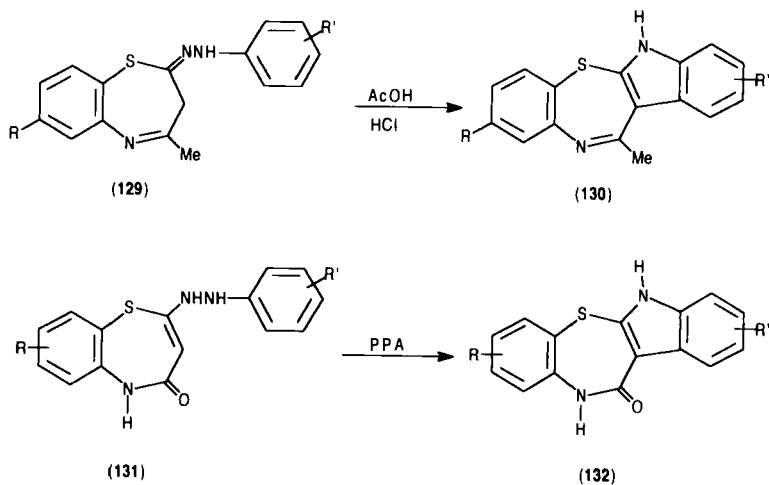


SCHEME 38



SCHEME 39

tively. Numerous reaction conditions (e.g., acetic acid saturated with hydrochloric acid, formic acid, polyphosphoric acid, or dilute sulfuric acid) were employed to perform the Fisher indole cyclization. Nevertheless, derivatives **130** were obtained, albeit in low yields (13–43%), only by refluxing **129** with acetic acid saturated with hydrochloric acid. Compounds **131** cyclized in hot polyphosphoric acid to give the desired tetracyclic compounds **132** (25–68% yields) (Scheme 40). Several derivatives



SCHEME 40

showed good activity against Gram-positive bacteria and *Cryptococci* (93MI2).

## 2. Indolo[2,3-*c*][1,5]benzothiazepines

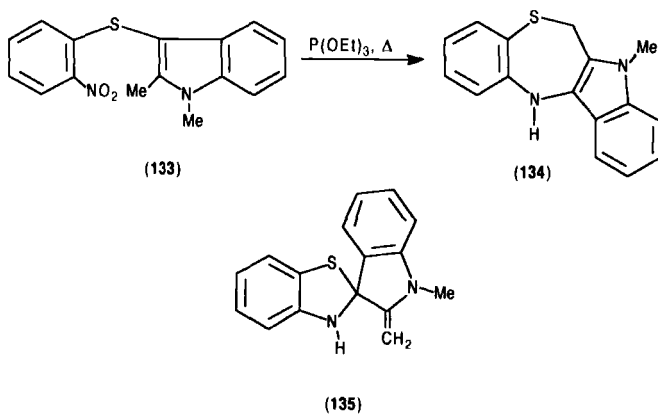
Deoxygenation of 1,2-dimethyl-3-(*o*-nitrophenylthio)indole (**133**) with an excess of triethyl phosphite, either neat or with cumene as solvent, at 160°C afforded indolo[2,3-*c*][1,5]benzothiazepine (**134**) in 34% yield. This product may arise via *ipso*-substitution by the initially formed nitrene to the 3-position of the indole nucleus to give the intermediate **135** (Scheme 41) [88JCR(S)272].

### B. BENZOFURO-1,5-BENZOTHAZEPINES

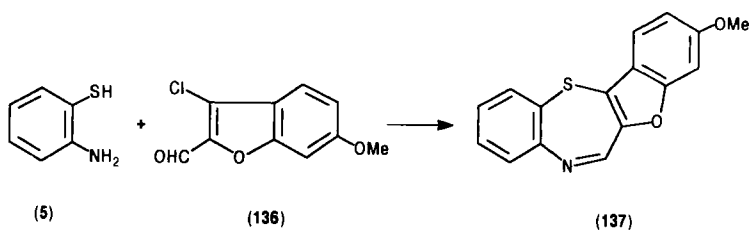
To date, only the benzofuro[3,2-*b*][1,5]benzothiazepine system is known.

#### 1. Benzofuro[3,2-*b*][1,5]benzothiazepines

Benzofuro[3,2-*b*][1,5]benzothiazepine (**137**) was obtained from 2-aminothiophenol (**5**) and 3-chloro-2-formyl-6-methoxybenzofuran (**136**) in acetonitrile containing potassium carbonate (Scheme 42) (87MI1).



SCHEME 41



SCHEME 42

### C. PYRAZOLOPYRIDO-1,5-BENZOTHAZEPINES

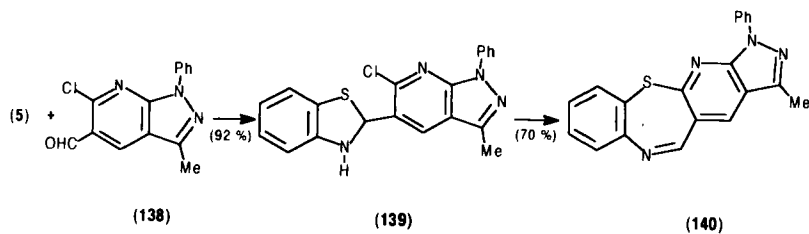
For these condensed 1,5-benzothiazepines, only one tetracyclic system has been reported.

#### 1. *Pyrazolo*[4',3':5,6]*pyrido*[2,3-*b*][1,5]*benzothiazepines*

A two-step synthesis of pyrazolo[4',3':5,6]pyrido[2,3-*b*][1,5]benzothiazepine (140) has been described (82JHC809): The condensation of 5 with 6-chloro-5-formylpyrazolo[3,4-*b*]pyridine (138) afforded the benzothiazoline derivative (139), which was then cyclized by refluxing in ethanolic sodium ethoxide to give 140 (Scheme 43). Spectroscopic data of compound 140 are also given.

### D. QUINO-1,5-BENZOTHAZEPINES

Two different quino-1,5-benzothiazepine ring systems have been exploited using a similar general synthetic route.



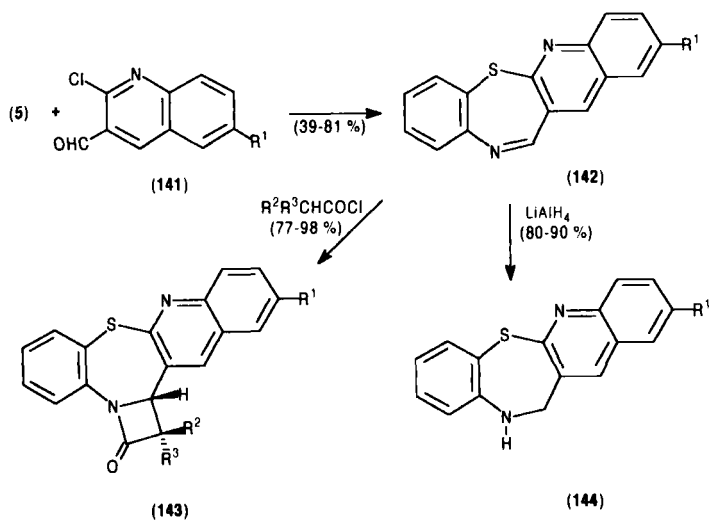
SCHEME 43

### 1. *Quino[2,3-*b*][1,5]benzothiazepines*

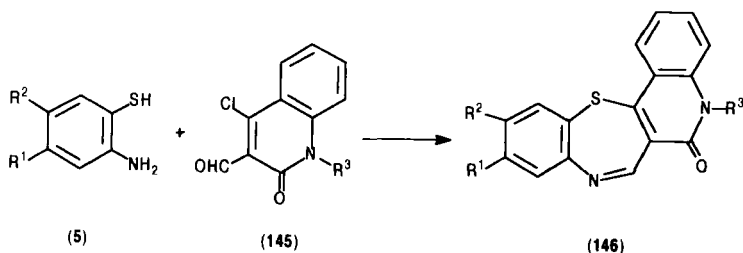
2-Chloro-3-formylquinolines (**141**) undergo cyclization with **5** in DMF in the presence of potassium carbonate at room temperature to give quino[2,3-*b*][1,5]benzothiazepines (**142**). The reduction of **142** with lithium aluminum hydride in ether afforded the corresponding 11,12-dihydro derivatives **144** [88H(27)401]. The same authors later reported the synthesis of condensed  $\beta$ -lactam derivatives of quino[2,3-*b*][1,5]benzothiazepines (**143**), which were obtained by reaction of **142** with acyl chlorides in the presence of triethylamine in refluxing benzene for 1 hour (Scheme 44) [90H(31)1867]. The most diagnostic feature in the  $^1\text{H-NMR}$  spectra of the pentacyclic derivatives **143** is the resonance of the  $\beta$ -lactam protons. On the basis of the low  $J_{13-13a}$  values present when  $\text{R}^3 = \text{H}$ , the *trans* stereochemistry was assigned to the  $\beta$ -lactam ring. The corresponding *cis* diastereomers were never detected.

### 2. *Quino[4,3-*b*][1,5]benzothiazepines*

As in the synthetic strategy reported in Scheme 41, quino[4,3-*b*][1,5]benzothiazepin-6(5*H*)-ones (**146**) were obtained in good yields by reaction of 4-chloro-3-formylquinolin-2(1*H*)-ones (**145**) with 2-aminothiophenol (Scheme 45) [93IJC(B)1063].



SCHEME 44



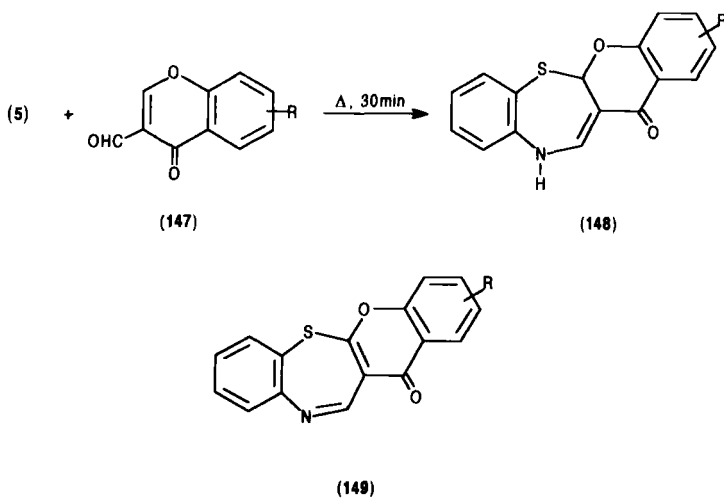
SCHEME 45

### E. BENZOPYRANO-1,5-BENZOTHAZEPINES

Three benzopyranobenzothiazepine systems, depending on the different annelation of the benzopyrano nucleus to the thiazepine ring, are known. The synthesis was generally achieved by condensation reaction of aminothiophenol with chromone or coumarin derivatives.

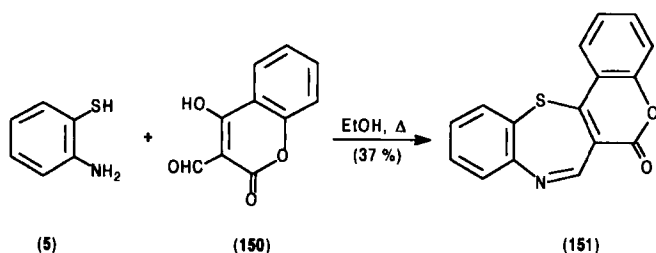
#### 1. [1]Benzopyrano[2,3-b][1,5]benzothiazepines

Cyclocondensation of 3-formyl-4*H*-1-benzopyran-4-ones (147) with 5 in refluxing benzene containing *p*-toluenesulfonic acid gave 5*a*,11-dihydro-13*H*-[1]benzopyrano[2,3-*b*][1,5]benzothiazepin-13-ones (148) in 70–81%



SCHEME 46





SCHEME 47

yields (79S337). Prolonged heating led to dihydro products **148** together with the corresponding dehydrogenated compounds **149**, thereby reflecting the ease with which the more conjugated product is formed from the dihydro derivative. In addition, dehydrogenation to **149** was easily effected in high yields (67–80%) by treating compounds **148** with chloranil in xylene (Scheme 46).

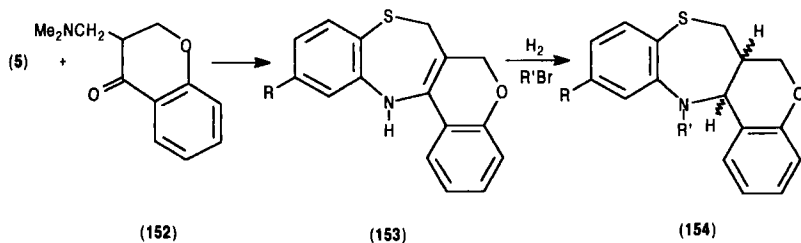
## 2. [1]Benzopyrano[4,3-b][1,5]benzothiazepines

Analogously, 6*H*-[1]benzopyrano[4,3-*b*][1,5]benzothiazepin-6-one (**151**) was obtained by a cyclocondensation reaction using 3-formyl-2*H*-1-benzopyran-2-one (**150**) and **5** (Scheme 47) (91M77).

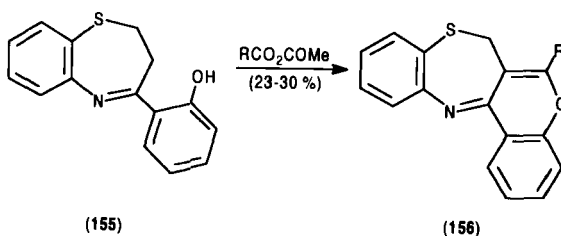
## 3. [1]Benzopyrano[3,4-*c*][1,5]benzothiazepines

7,13-Dihydro-6*H*-[1]benzopyrano[3,4-*c*][1,5]benzothiazepines (**153**) were prepared by cyclocondensation of **5** with 2,3-dihydro-3-dimethylaminomethyl-4*H*-1-benzopyran-4-one (**152**). Compounds **153** were reduced and alkylated to derivatives **154**, which demonstrated sedative and muscle-relaxant activities (Scheme 48) (73FRP2150807).

The synthesis of 7*H*-[1]benzopyrano[3,4-*c*][1,5]benzothiazepines (**156**)



SCHEME 48



SCHEME 49

was carried out by heating 2,3-dihydro-4-(2-hydroxyphenyl)-1,5-benzothiazepines (**155**) with various acid anhydrides (Scheme 49) (74LA328).

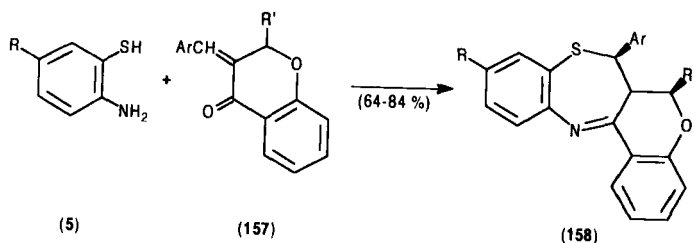
6a,7-Dihydro-6H[1]benzopyrano[3,4-c][1,5]benzothiazepines (**158**) were synthesized by a one-step cyclization of 2-aminothiophenols with unsaturated ketones **157** in anhydrous toluene using trifluoroacetic acid as the catalyst (Scheme 50) [81MI1; 82OMR133; 83MI1; 93IJC(B)869]. The stereochemistry, studied by means of  $^1\text{H}$ -NMR spectroscopy, revealed that the aryl group at position 7 is equatorial and the hydrogen atoms at the two adjacent carbon atoms C-6a and C-7 adopt a *trans* arrangement.

## F. BENZOTHIOPYRANO-1,5-BENZOTHAZEPINES

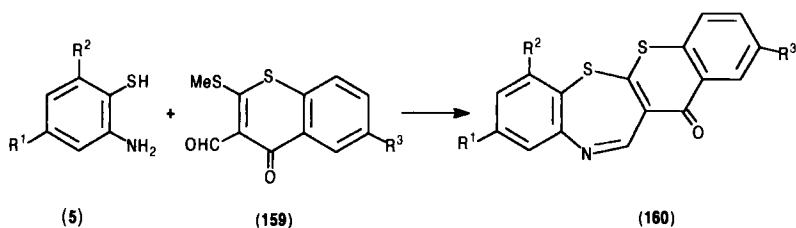
Like the benzopyrano derivatives, the benzothiopyrano-1,5-benzothiazepines have been obtained; in particular the [3,4-*c*] system was studied.

### 1. [1]Benzothiopyrano[2,3-*b*][1,5]benzothiazepines

3-Formyl-2-methylthio-4H-1-benzothiopyran-4-one (**159**) reacted with 2-aminothiophenols to give 13H-[1]benzothiopyrano[2,3-*b*][1,5]benzothiazepin-13-ones (**160**) (Scheme 51) (92MI3).



SCHEME 50



SCHEME 51

## 2. [1]Benzothiopyrano[3,4-c][1,5]benzothiazepines

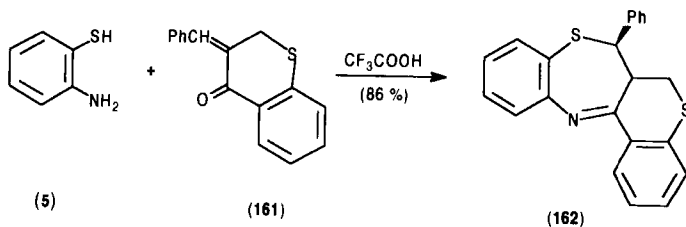
The synthetic approach reported in Scheme 50 has also been applied to the synthesis of 6a, 7-dihydro-6*H*[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (**162**) starting from **5** and 3-phenylmethylene-4*H*-1-benzothiopyran-4-one (**161**) (Scheme 52) (81MI1; 82OMR133; 83MI1). <sup>1</sup>H-NMR investigations proved that the phenyl group at C-7 exists in a quasi-equatorial position, analogous to that in the isosteric benzopyrano derivatives.

## G. QUINAZOLINO-1,5-BENZOTHIAZEPINES

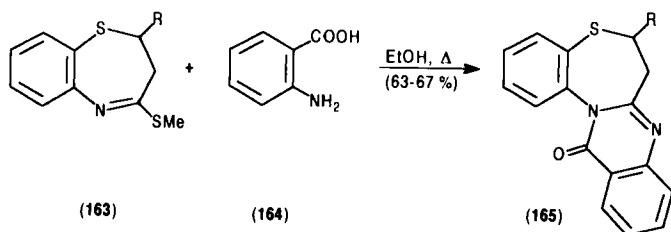
Only one synthetic approach to the quinoxalino-1,5-benzothiazepine system has been reported.

### 1. Quinazolino[2,3-*d*][1,5]benzothiazepines

6,7-Dihydro-13*H*-quinazolino[2,3-*d*][1,5]benzothiazepin-13-ones (**165**) were synthesized by reaction of 2,3-dihydro-4-methylthio-1,5-benzothia-



SCHEME 52



SCHEME 53

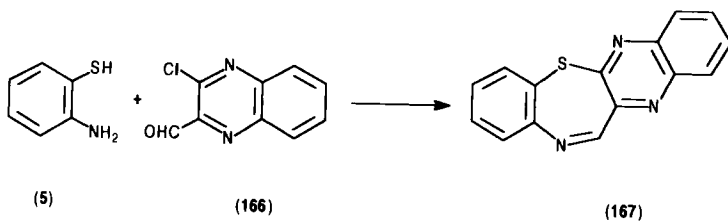
zepines (163) with 2-aminobenzoic acid (164) in a one-step procedure (Scheme 53) (88JHC1399; 89MI2).

## H. QUINOXALINO-1,5-BENZOTHAZEPINES

For quinoxalino-1,5-benzothiazepines, only one example has been reported concerning the synthetic approach to the [2,3-*b*] system.

### 1. Quinoxalino[2,3-*b*][1,5]benzothiazepines

Quinoxalino[2,3-*b*][1,5]benzothiazepine (167) was prepared by a reaction of 5 with 3-chloroquinoxalino-2-carboxaldehyde (166) in ethanolic sodium hydroxide followed by acid-catalyzed cyclocondensation (Scheme 54) (90ZC251).



SCHEME 54

## ACKNOWLEDGMENTS

We express our appreciation to Mr. Claudio Scambia for his help in drawing the formulas.

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## Recent Developments in the Chemistry of Pyrido[1,2-*a*]pyrimidines

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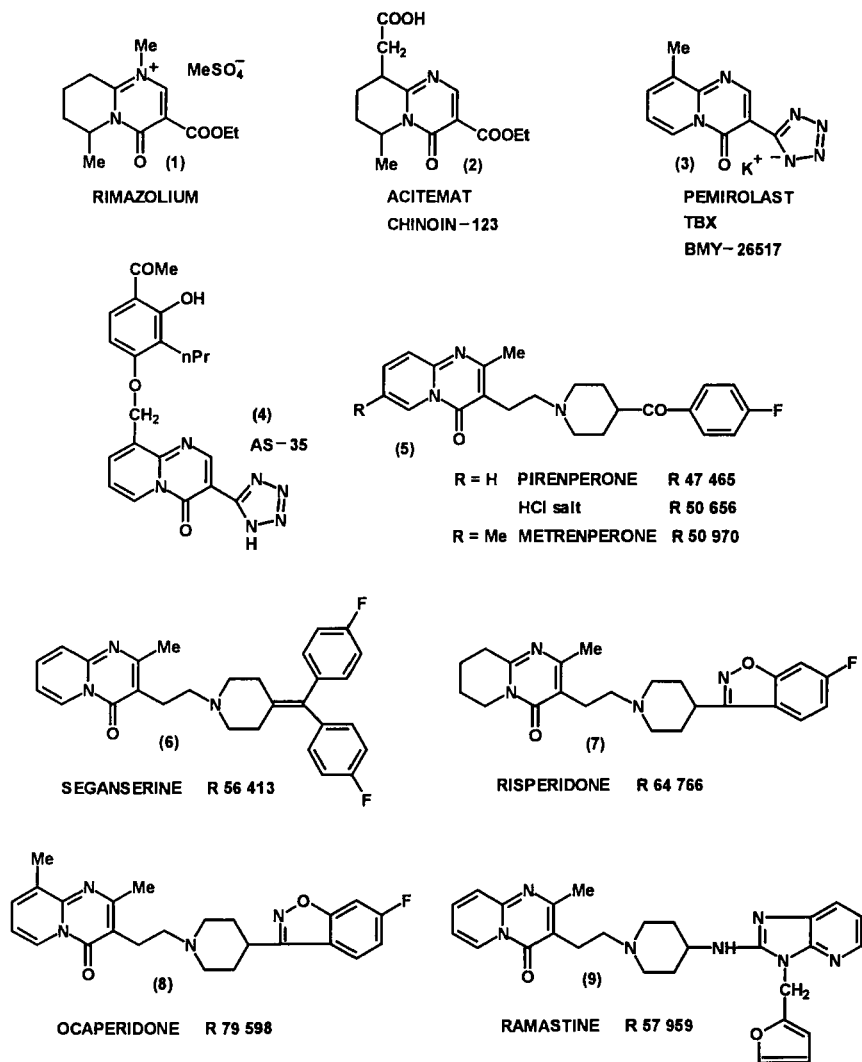
## I. Introduction

The chemistry of the pyrido[1,2-*a*]pyrimidines was reviewed in 1983 (83AHC241; 85MI3). This earlier review covered the chemical literature through the first half of 1981 and surveyed 469 publications. In the last 12 years the appearance of another 500 papers and patents indicates the increasing interest in these compounds.

Pyrido[1,2-*a*]pyrimidines represent a simple bicyclic ring system that contains a nitrogen-bridgehead condensed pyrimidine moiety. Synthetic methods for these compounds can often be applied to the preparation of similar bi- and polycyclic ring systems (e.g., benzologs, *N*-analogs, five membered congeners, and so on) and their reactivities are sometimes similar to those of the above-mentioned derivatives.

The representatives of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines, which exhibit valuable biological activities, have aroused much interest (88MI8). Their pharmacological activities have been examined intensively, and the therapeutic effects of some of them have been demonstrated in clinics. Formulas of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines with outstanding pharmacological activities are depicted in Scheme 1. Other representatives of 4*H*-pyrido[1,2-*a*]pyrimidines are used as photographic sensitizers, catalysts for curing polyisocyanates, or as dyes for acrylic nylon, polyester fibers, and photographic materials.

This article covers the primary chemical literature published between the second half of 1981 and 1993 and contained in *Chemical Abstract Chemical Substance Indexes*, Volumes 95–119 inclusive. Pertinent 1994 literature is also included. In the following sections the physicochemical and spectroscopic properties, syntheses, reactions, and more briefly, the

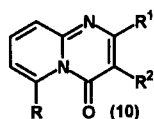


SCHEME 1

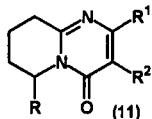
utilization of pyrido[1,2-*a*]pyrimidines are discussed. Within each individual section we review the pyrido[1,2-*a*]pyrimidines salts, the 2-oxo-2*H*-, 4-oxo-4*H*-, and then the 6-oxo-6*H*-pyrido[1,2-*a*]pyrimidines, followed by the 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines, the 2-oxo-3,4-dihydro-2*H*- and 4-oxo-2,3-dihydro-4*H*-pyrido[1,2-*a*]pyrimidines, and finally miscellaneous pyrido[1,2-*a*]pyrimidines.

## II. Physicochemical Properties of Pyrido[1,2-*a*]pyrimidines

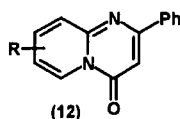
The solubilities of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**10–12**) were determined in water, ethanol, and *n*-octanol at  $298 \pm 1^\circ\text{K}$  by a spectrophotometric method (86MI2). Both the saturation of the pyridine ring and the presence of a methyl group at position 3 increase solubilities.



R - R<sup>2</sup> = H, Me



R - R<sup>2</sup> = H, Me

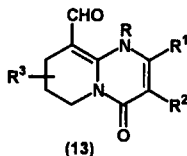


R = Me

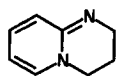
The protonation constants of 20 alkyl-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and their 6,7,8,9-tetrahydro derivatives were measured in water (83MI2; 85MI12; 86MI13) and in water containing 15, 30, 45, and 60% ethanol (85MI12; 86MI13) by Calvin's potentiometric method; and they were estimated according to the Hammett linear free energy relationship (84MI13). A good linear regression was found between the basic strength of unsaturated 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and their gas-phase protonation energy calculated by the semiempirical CNDO/2 method (86MI15; 87ST59). The  $pK_a$  values of the N-1 atom and 3-carboxyl group of 15 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids and esters and their saturated derivatives were determined by spectrophotometric and potentiometric methods (87MI11).

Zinc- and silver-ion coordination equilibria of 15 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines-3-carboxylic acid derivatives with different degrees of saturation were investigated by polarographic, potentiometric, and spectrophotometric method (87MI14).

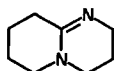
The protonation of 9-formyltetrahydropyrido[1,2-*a*]pyrimidin-4-ones **13** occurred at the oxygen atoms of the formyl group according to  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR spectroscopy [86JCS(P2)1911; 88MI7].



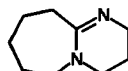
The basicity of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine **14** was about half of that of diazabicycloundecene (DBU) **16**, while that of 3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine **15** was twice of that of DBU in acetonitrile (85C269).



(14)



(15)

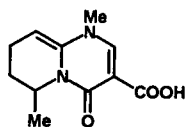


(16)

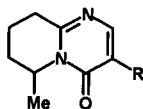
The octanol–water (pH 5) partition coefficients of alkyl-substituted 4*H*-pyrido[1,2-*a*]pyrimidines-4-ones **10** and **11**, 3-phenyl and 3-ester derivatives ( $R^2 = \text{Ph, COOEt}$ ), and some tetra- and hexahydro derivatives were determined by the classical shake-flask technique at ambient temperature (81MI4; 82MI9). Hansch-type  $\pi$  values of the substituent ( $R-R^2$ ) were also calculated. The apparent octanol–water partition coefficients of seganserine **6** and its 7-methyl derivative were measured (88MI14). The  $pK_a$  values and apparent octanol–water partition coefficients (at pH 7.4) of risperidone **7** (92MI20, 92MI30), its 9-hydroxy derivative (92MI30), and ocaperidone **8** were reported (92MI20).

An excellent correlation was determined between octanol–water partition coefficients of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **10** and **11** ( $R = \text{H, Me, Et}$ ;  $R^1 = \text{H, Me, Et, } n\text{Pr}$ ;  $R^2 = \text{H, Me, Et, Pr}$ ) and their  $R_M$  values measured by TLC on Kieselgel 60  $F_{254}$  plates with a methanol–water (30 : 70) mobile phase (82MI9).

The chromatographic behavior of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and their 6,7,8,9-tetrahydro derivatives was studied on silanized silica gel layers using a aqueous mobile phases by TLC in normal chambers, and by OPTLC in a pressurized ultramicrochamber (88MI1–88MI3; 89MI10; 90MI1).

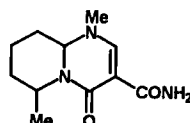


(17)



(18)

$R = \text{COOEt}$   
 $\text{COOH}$   
 $\text{H}$



(19)

Rimazolium **1** and its potential metabolites **17** and **18** ( $R = \text{COOEt}$ ) were separated by means of TLC on Silica Gel 60  $GF_{254}$ , using a 95 : 7.5 : 11 mixture of chloroform, methanol, and acetic acid as eluent (81MI3).

4*H*-Pyrido[1,2-*a*]pyrimidin-4-one, its 6,7,8,9-tetrahydro derivatives, and their monomethylated derivatives were characterized by gas-chromatographic (GC) retention indices measured on apolar and medium-polar stationary phases (91MI4). Kováts' retention indices of alkyl-substituted 4*H*-pyrido[1,2-*a*]pyrimidines-4-ones and some 6,7,8,9-tetrahydro

derivatives were determined by GC on four stationary phases (OV-1, OV-17, OV-25, and Carbowax 20M). A good linear correlation was found between octanol/water partition coefficients and  $\Delta I$  values (81MI2; 82MI1, 82MI9; 83MI10).

Good correlations were also found between molecular connectivity indices of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and their partition coefficients and chromatographic parameters (83MI7, 83MI9). Molar refractions (RM) of five 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were determined in dioxane, and a good correlation was found between RMs and gas-chromatographic retention indices (*I*) (87MI2).

A headspace GC determination of acetone, ethanol, and methyl ethyl ketone residues in acitemat (**2**) was developed by using OV-1 Chromosorb WHP and flame-ionization detection (89MI7).

Liquid-chromatographic properties of different 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were investigated by reverse-phase HPLC (84MI5, 84MI15, 84MI16), reverse-phase ion-pair chromatography (85MI26), ion exchange HPLC (84MI16), and normal ion-pair chromatography (85MI21).

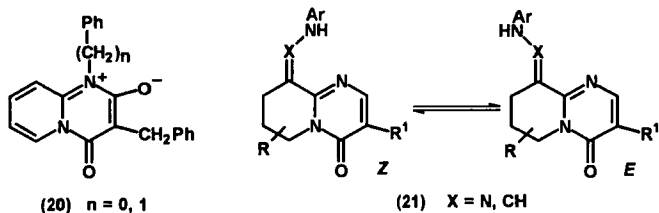
Good linear correlations were found between octanol–water partition coefficients and different HPLC retention indices (*k'*) (84MI5, 84MI15, 84MI16; 86MI23).

For the determination of the blood level of pemirolast **3**, a sensitive reversed-phase HPLC method was developed by using fluorescent detection and a 7-methyl derivative of pemirolast as internal standard (87JPS918). The blood levels of acitemat **2** and its main metabolite (the dicarboxylic acid) were determined in human serum by micro-HPLC on a Zorbax C8 column (86MI18). An HPLC method was developed for determination of Chinoin-127 **19** and its metabolites in rat and human serum and rat urine using 6-desmethyl derivative of Chinoin-127 (86MI19). The levels of risperidone **7** and its major 9-hydroxyl metabolite were determined in plasma, urine, and animal tissues by an HPLC method using a reverse-phase column (92MI30; 93MI19). A high-sensitivity HPLC method with electrochemical detection for the determination of risperidone **7** in human plasma was also developed (93JPS447).

The X-ray and photoelectron spectra of mesoionic pyrido[1,2-*a*]pyrimidinones **20** were investigated (82MI2).

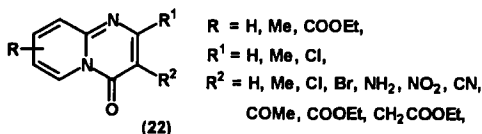
2,4-Dimethyl-9-hydroxypyrido[1,2-*a*]pyrimidinium perchlorate and its metal complexes were characterized by UV and IR spectroscopy (90MI24).

The UV and IR spectra of 9-arylhydrazono- and 9-arylaminomethylene-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidinones **21** (X = N, —CH=) were studied. The fast *E*–*Z* isomerization of the substituent at position 9 was influenced by the nature of the solvent and by the substituents on

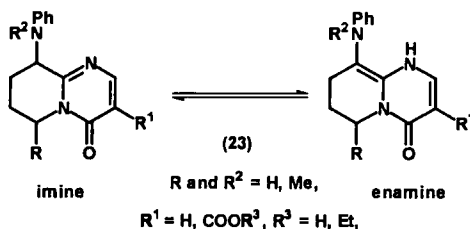


the aryl and pyridopyrimidine rings (85ACH305). The ionization of compounds **21** was investigated at different pH values, and the correct structures were selected by Pariser–Parr–Pople (PPP) calculations from the different ionized models (85ACH321).

The characteristic features of the UV and IR spectra of 43 unsaturated 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **22** were systematically studied. The negative solvent effect of the lowest-energy  $\pi$ – $\pi^*$  transition was investigated by the PPP quantum-chemical method (85JHC481).



The UV spectra of 9-(phenylamino)tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **23** indicated the presence of an imine–enamine type of tautomerism in solution. A carboxyl or ester group in position 3 ( $R^1 = COOR^3$ ;  $R^3 = H, Et$ ) and a methyl group in position 6 ( $R = Me$ ) shifted the equilibrium toward the enamine form in a polar solvent [85JCS(P1)1015]. For the imine tautomer, UV maxima at 235–250 nm and 280–300 nm and for the enamine absorbances at 260–265 nm and 355–365 nm are characteristic.



Generally 2-oxo-2*H*- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (83AHC-241) and their tetrahydro derivatives (82JHC909, 82MI4) can be distinguished by UV, IR, and  $^1H$  NMR spectra (91UKZ172).



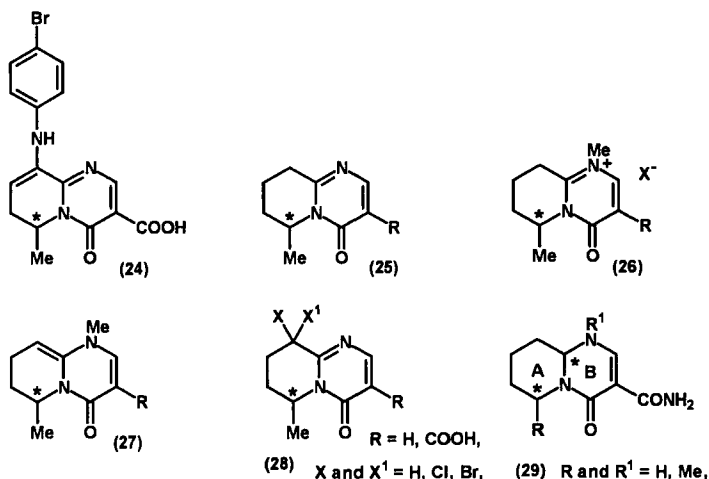
The molar extinction ratio ( $\epsilon_{280-330}/\epsilon_{230-245}$ ) at the indicated wavelengths is usually higher than 1 for 4-oxo derivatives, and less than 1 for 2-oxo compounds (82JHC909, 82MI4). However, the above differences in UV spectra are diminished when the 1,6,7,8-tetrahydro tautomeric form of tetrahydro derivatives is predominant owing to stabilization due to the presence of a suitable substituent (i.e., formyl group) at position 9 [85JCS(P2)1873] (Table I).

Kajtár and co-workers studied the UV and CD spectra of different optically active 6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **24–29**. The absolute configuration was determined by an X-ray investigation of 9-(4-bromophenyl)amino derivatives (**24**) [83JCS(P2)1413]. The results of CNDO/S calculations for energies, oscillator strengths, and rotational strengths due to the transitions of simple models with geometries based on X-ray data were in good qualitative agreement with the experimental UV and CD spectra, and allowed the chiroptical properties of compounds **25–27** to be correlated with their known absolute geometries. The analysis of the experimental UV and CD spectra indicated that 6,7,8,9-tetrahydro derivatives **25** and **26** contain a chromophoric system analogous to the cyclically conjugated system of 3-methylpyrimidin-4(3*H*)-one, which is a

TABLE I  
CHARACTERISTIC UV DATA OF SOME 2-OXO-2*H*-  
AND 4-OXO-4*H*-PYRIDO[1,2-*a*]PYRIMIDINES  
[85JCS(P2)1873]

286 nm ( $\epsilon_a$ 4848) 241 nm ( $\epsilon_b$ 11,818) $\epsilon_a/\epsilon_b < 1$	302 nm ( $\epsilon_a$ 7680) 229 nm ( $\epsilon_b$ 5450) $\epsilon_a/\epsilon_b > 1$
361 nm ( $\epsilon_a$ 19,550) 312 nm ( $\epsilon$ 9380) 268 inf ( $\epsilon$ 1880) 223 nm ( $\epsilon_b$ 11,700)	361 nm ( $\epsilon_a$ 21,800) 320 inf ( $\epsilon$ 8300) 271 nm ( $\epsilon$ 3600) 223 nm ( $\epsilon_b$ 12,200)

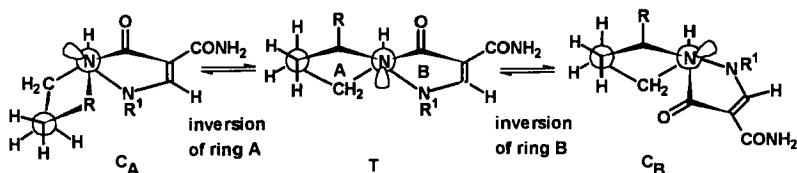
Note: inf = inflexion.



heteroaromatic derivative of the benzyl anion. For the 1,6,7,8-tetrahydro derivatives **27**, a divinylamine chromophore was assigned.

Investigations of the chiroptical properties of 9-halogen derivatives of 6-methyltetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **28** (X and X' = Cl, Br) established that the sign of the most characteristic CD bands is determined by the axial halogen atom in position 9 to the inherently achiral pyrimidinone chromophore (87JHC393).

The homochiral 6-methyl and 1,6-dimethylhexahydropyridopyrimidin-4-ones **29** (R = Me, R' = H and Me) exhibited enantiomeric CD spectra (85JOC2918). X-Ray investigations revealed that *N*-desmethylhexahydropyridopyrimidine **29** (R = Me; R' = H) contains a transoid ring junction (T), while the 1-methyl derivatives **29**, (R = R' = Me) adopts a cisoid one (C<sub>B</sub>) in which the geometry of the inherently chiral chromophore, the pyrimidinone ring, is almost the reverse of that of the former (see Scheme 2). (The other cisoid conformer, C<sub>A</sub>, is highly unfavorable because of the presence of an equatorial 6-methyl group.) The conformational change of the pyrimidinone ring of 1-methyl-substituted hexahydropyrido[1,2-*a*]pyrimidinone **29** (R = R' = Me) avoids an unfavorable steric interfer-



SCHEME 2. The possible conformations of hexahydropyrido[1,2-*a*]pyrimidin-4-ones (**29**). (The bonds N(5)—C(9a) and C(7)—C(8) are perpendicular to the plane of the paper.)

ence between the N(1)-methyl group and the hydrogen atoms (mostly the equatorial one) at the C(9) methylene group in the conformer with a transoid ring junction (T). This also was confirmed by a calculation using the EENYC method.

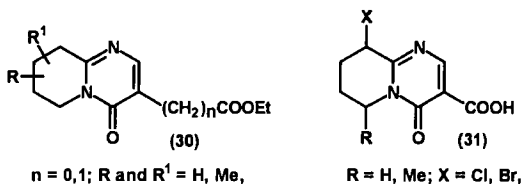
The characteristic electronic and chiroptical properties of hexahydro-pyrido[1,2-*a*]pyrimidin-4-ones **29** were qualitatively characterized by quantum-chemical calculations in the CNDO/S-CI approximation on some simplified models having the geometries of the molecules studied (80MI2; 85JOC2918).

A linear relationship was established between 4-carboxyl bond length (as determined by X-ray diffraction) and IR vibration frequency in a series of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (78ACH1819).

The magnitudes of the coupling frequency of the 1,3-dicarbonyl moiety of 4-oxo-4*H*-, 6,7,8,9-tetrahydro-, 1,6,7,8,9,9a-hexahydro-, and perhydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates are characterized by shifts and by the intensity differences of the coupled vibration bands in their IR spectra (92MI11).

In the IR spectra the  $\nu_{4\text{-CO}}$  band of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones appears at higher wavenumbers than the  $\nu_{2\text{-CO}}$  band of 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (92HCA1262). In the  $^1\text{H}$  NMR spectra of 6-unsubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones the chemical shift of H-6 is located downfield by about 1 ppm as compared with the corresponding signal of 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (92HCA1262). The spectral  $\nu_{\text{CO}}$  band of *N,N*-disubstituted 2-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones appeared between 1660 and 1675  $\text{cm}^{-1}$ , while that of the isomeric *N,N*-disubstituted 4-amino 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones can be found between 1630 and 1645  $\text{cm}^{-1}$  in chloroform (82FES747; 87JHC329; 88FES705). In the  $^1\text{H}$  NMR spectra of isomeric 2-amino-4-oxo-4*H*- and 4-amino-2-oxo-2*H*-pyrido[1,2-*a*]pyrimidines the chemical shifts of 3-H (5.25–5.65 ppm and 6.10–6.55 ppm, respectively) and 6-H (8.80–8.95 ppm and 7.95–8.40 ppm, respectively) are characteristically different in a mixture of  $\text{CDCl}_3$ –DMSO- $d_6$  (82FES747; 87JHC329; 88FES705).

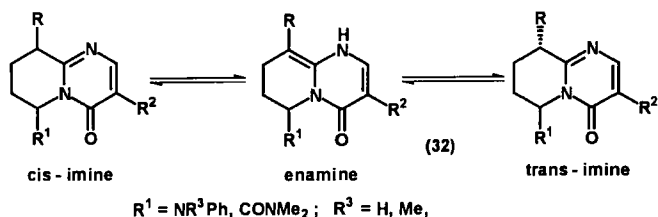
Conformational analysis of 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetates and -3-carboxylates **30** ( $\text{R} = \text{H}$ ) and their monomethylated ( $\text{R} = \text{Me}$ ,  $\text{R}^1 = \text{H}$ ) and 6,9-, 7,9-, and 8,9-dimethylated derivatives were carried out by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy (86JOC394). At ambient temperature the 6-methyl derivatives predominantly adopt the energetically most favorable half-chair conformation with a pseudoaxial methyl group. In the other half-chair conformation a serious 1-3 allylic strain exists between the pseudoequatorial methyl group and the adjacent carbonyl group. At the 7- and 8-methyl derivatives the half-chair conformations with equatorial methyl group occur almost exclusively, but the 9-



methyl derivatives exist in essentially equally populated half-chair conformers with pseudoaxial and pseudoequatorial methyl groups. In the dimethyl series *trans*-6,8-, *cis*- and *trans*-6,9-, -7,9, and *cis*-8,9-dimethyl derivatives exist primarily in a single conformation because of unfavorable steric interactions in the alternative half-chair conformation. The *trans*-8,9-dimethyl derivative contains about a 3 : 1 equilibrium mixture of half-chair conformations containing the methyl groups in diequatorial and diaxial positions, respectively. In the *cis*-6,8-dimethyl derivative both half-chair conformations are very destabilized by steric crowding, so this derivative adopts an envelope, or skew-boat, conformation in which the 6-methyl group is out of the plane of neighboring amide group. In  $^{13}\text{C}$  NMR the 7- and 8-methyl substituent parameters are similar to those found in 2-methyltetralines, but the 6- and 9-methyl substituent parameters are quite different from those found in 1-methyltetralines.

Conformational analysis of some 9-chloro- and 9-bromo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **31** and their 9,9-dichloro and 9,9-dibromo derivatives was also carried out by  $^{13}\text{C}$  NMR spectroscopy (83JHC619). The halogen atoms in the 9-chloro and 9-bromo derivatives **31** ( $R = H$ ) in the predominantly half-chair conformation occupy the pseudoaxial position. This conformer is probably stabilized by a favorable orbital interaction, while the other one, with a pseudoequatorial halogen atom, is destabilized by the unfavorable dipole-dipole interaction between the 9-halogen and  $\text{C}(9a)=\text{N}(1)$  bonds. The methyl group in the 6-methyl derivatives in predominantly half-chair conformations is in the pseudoaxial position (83JHC619).

The imine-enamine tautomerism of 9-aminotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **32** ( $R = \text{NR}^3\text{Ph}$ ,  $R^3 = H, Me$ ) were studied by  $^1\text{H}$  and

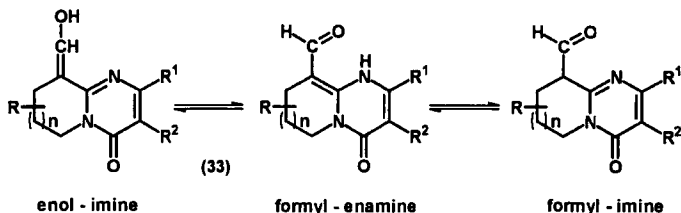


$^{13}\text{C}$  NMR [85JCS(P1)1015]. In equilibrium mixtures the ratio of the enamine form increased in  $\text{DMSO-d}_6$  compared to that in  $\text{CDCl}_3$ , and in the presence of an electron-withdrawing group in position 3 (i.e.,  $\text{R}^2 = \text{COOH}$ ,  $\text{COOEt}$ ) or in the presence of a methyl group in position 6 ( $\text{R}^1 = \text{Me}$ ).

For 9-phenylamino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **32** ( $\text{R} = \text{NHPh}$ ;  $\text{R}^1 = \text{H}$ ;  $\text{R}^2 = \text{H}$ ,  $\text{COOH}$ ) the half-chair conformation with a pseudoaxial 9-phenylamino group was the predominant one. But with the 6-methyl-9-phenylamino derivatives **32** ( $\text{R} = \text{NHPh}$ ,  $\text{R}^1 = \text{Me}$ ) the *cis-trans* ratio was near 1 : 1 in the imine form. The presence of a methyl group on the nitrogen atom of the 9-anilino group **32** ( $\text{R} = \text{NMePh}$ ) increased the amount of the *cis* form which contained the 9-substituent in a pseudoequatorial position [85JCS(P1)1015]. The 6-methyl group was in a pseudoaxial position in all tautomers.

In  $\text{CDCl}_3$  9-(*N,N*-dimethylaminocarbonyl)-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **32** ( $\text{R} = \text{CONMe}_2$ ) exist as equilibrium mixtures of *cis*- and *trans*-imine tautomers with a slight excess of the *cis* forms. The structure of these compounds was investigated by  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR. The interconversion between *cis* and *trans* imine forms occurs through the enamine tautomer, which could not be identified. The 6-methyl group occupies the pseudoaxial position in all compounds. The *cis* and *trans* forms could be distinguished by  $^{15}\text{N}$  data for the (dimethylamino)carbonyl group, too. In a pseudoaxial orientation of the (dimethylamino)carbonyl group the shielding is approximately 2.5 ppm higher than that in a pseudoequatorial orientation, which may be a result of steric interactions (82OMR229).

The structure of 9-formyltetrahydropyrido[1,2-*a*]pyrimidin-4-ones **33** ( $n = 1$ ) and the piperidine-ring homologs ( $n = 0, 2, 3$ ) was investigated by  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR spectroscopy [83JCS(P1)369, 83JCS(P2)1153; 85JCS(P2)1873, 85JCS(P2)1881]. The formyl derivatives exhibit a ring-size-dependent tautomerism between enol-imine, formyl-enamine and formyl-imine forms (91MI2, 91MI3). For example, 9-formyl-4-oxotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **33** ( $n = 1$ ,  $\text{R} = \text{R}^1 = \text{H}$ ,



$R^2 = \text{COOEt}$ ) exists as about a 9 : 1 mixture of formyl-enamine and enol-imine tautomers.

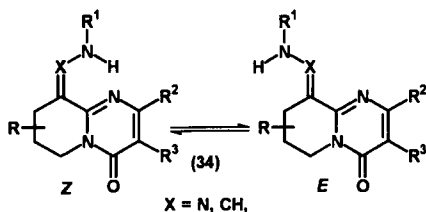
For all 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones the formyl-enamine is the predominant form both in solid and solutions [83JCS(P1)369, 83JCS(P2)1153; 85JCS(P2)1873, 85JCS(P2)1881].

Protonation of 9-formyltetrahydropyrido[1,2-*a*]pyrimidinones takes place at the formyl oxygen, and the protonated enol-imine tautomers on the N(1) atom became the predominant tautomer forms [86JCS(P2)1911]. Similar phenomena were observed for the 9-formyltetrahydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones and their homologs [85JCS(P2)1873; 88MI7].

The 9-benzoyl- and 9-[(ethoxycarbonyl)carbonyl]tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones also exhibit predominantly the 1,6,7,8-tetrahydro tautomeric forms in solution [85JHC593; 89JCS(P2)1613].

The structures of hydroxylated metabolites of 3-ethyl-2,6-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were determined on the basis of mass spectrometry and NMR spectroscopy (89MI13).

The antiallergic 9-hydrazono- and 9-aminomethylene-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **34** exhibit a solvent-dependent *E*-*Z* isomerism if the amino group of the hydrazino or aminomethylene group is unsubstituted or monosubstituted. In  $\text{CDCl}_3$  the predominant and sterically crowded *Z* isomers are stabilized by an internal hydrogen bond between the amino group and N(1) ring atom, while in  $\text{DMSO-d}_6$  (a solvent that forms a stronger hydrogen bridge with the amino group) generally the sterically more favorable *E* form is predominant [83JCR(S)161, 83JCS(P2)165, 83JCS(P2)1409, 83OMR687]. However, if a methyl group is present at position 8 of the pyridopyrimidine ring, the *E* form also becomes sterically crowded, and therefore the *Z* forms are also favorable in  $\text{DMSO-d}_6$  (see Table II).



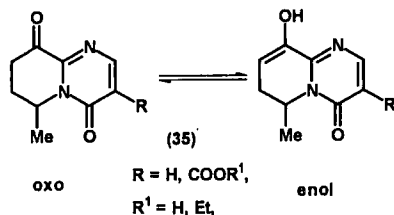
Because a  $\text{C}=\text{C}$  double bond is longer than a  $\text{C}=\text{N}$  double bond (72MI1), steric interaction between the 8-methyl and the  $\text{PhNH}$  groups in the *E* form of a 9-phenylaminomethylene derivative is less than in that

TABLE II  
THE RATIO OF *E* AND *Z* GEOMETRIC ISOMERS OF  
ETHYL 9-(PHENYLHYDRAZONO)- AND 9-  
(PHENYLAMINO)METHYLENE-4-OXO-6,7,8,9-  
TETRAHYDRO-4*H*-PYRIDO[1,2-*a*]PYRIMIDINE-3-  
CARBOXYLATES (34, R<sup>1</sup> = Ph; R<sub>2</sub> = H;  
R<sup>3</sup> = COOEt) IN SOLUTION

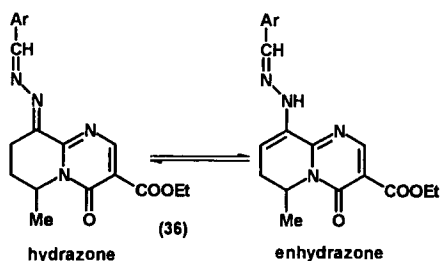
R	X	In CDCl <sub>3</sub>		In DMSO-d <sub>6</sub>	
		E%	Z%	E%	Z%
H	N	7	93	82	18
H	CH	6	94	75	25
6-Me	N	20	80	83	17
6-Me	CH	28	72	88	12
7-Me	N	5	95	83	17
7-Me	CH	14	86	84	16
8-Me	N	0	100	25	75
8-Me	CH	8	92	50	50

of a 9-phenylhydrazono derivative. Therefore, an increased amount of *E* form was detected for the 8-methyl-9-phenylaminomethylene derivative **34** (R = 8-Me; R<sup>1</sup> = Ph; R<sup>2</sup> = H; R<sup>3</sup> = COOEt). Because there is no possibility for the formation of a hydrogen bond, the disubstituted amino derivatives of the hydrazono and aminomethylene derivatives exist as the *E* geometric isomer regardless of the nature of the solvent [83JCS(P2)1409; 91MI1, 91MI2)].

4,9-Dioxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines **35** exhibit an oxo–enol tautomerism, which was studied by UV, IR, and NMR methods (85JHC1253). In the solid phase enol tautomers are present, while in a polar solvent an electron withdrawing substituent at position 3 shifts the equilibrium toward the enol form. The analogous 9-amino derivatives exist exclusively as 9-amino-6,7-dihydropyrido[1,2-*a*]pyrimidin-4-ones.



In  $\text{CDCl}_3$ , 9-(arylmethylenehydrazono)-6,7,8,9-tetrahydro-4*H*-pyrido [1,2-*a*]pyrimidin-4-ones **36** exist as an equilibrium mixture of hydrazone



and enhydrazone tautomers (91JHC781). A fair linear correlation exists between the logarithms of the equilibrium constants and Hammett  $\sigma_m$  and  $\sigma^-$  constants of the substituents present on the phenyl ring. The presence of an electron-withdrawing substituent on the phenyl group increases the amount of the enhydrazone tautomer. In some cases the respective tautomers were separated.

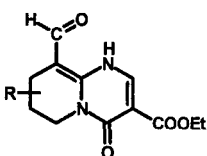
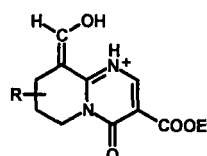
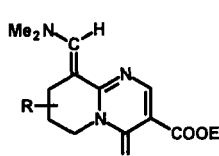
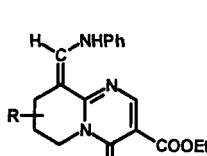
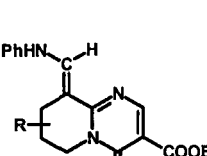
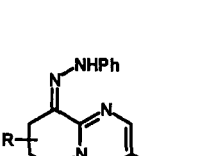
Tóth and co-workers measured  $^{15}\text{N}$  chemical shifts of different tetrahydro-, 1,6,7,8,9,9a-hexahydro-, and perhydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (see Table III and IV and Scheme 3) in  $\text{CDCl}_3$  [82JOC4780, 82OMR229; 83JCS(P2)1153, 83JCS(P2)1409, 83OMR687; 85JCS(P1)1015, 85JCS(P2)1881, 85JOC2918; 86JCS(P2)1911]. The  $^{15}\text{N}$  chemical shifts were determined relative to the signal of external  $\text{K}^{15}\text{NO}_3$  ( $\delta -3.55$ ) and then converted to relate to that of external neat nitromethane ( $\delta 0.0$ ).

The structures of some pyrido[1,2-*a*]pyrimidin-4-ones (**29**, **37–45**) were determined by X-ray investigations (Scheme 4) [83JCS(P1)369, 83JCS(P2)1413; 83AX(C)472, 85JOC2918; 86AX(C)573; 88JCS(P1)2993, 88JCS(P2)1287; 91T675]. Table V shows the bond distances and bond angles of some unsaturated pyrido[1,2-*a*]pyrimidines.

For the structure of malonyl- $\alpha$ -aminopyridine, the reaction product of 2-aminopyridine and diethyl malonate (24CB1168), different forms were suggested (83AHC241). Katritzky and Warring depicted the mesoionic form **37** on the basis of UV investigations (62JCS1544). Within the mesoionic structure **37**, different canonical forms were considered. The X-ray investigations of malonyl- $\alpha$ -aminopyridines **36** and **37** by Thorup and Simonsen confirmed [85AX(C)472; 86AX(C)573] the suggestion that the formula **46** represents most correctly the structure of this type of compound. The bond lengths of the C(9a)—N(1) and C(9a)—N(5) units and the C(2)—C(3) and C(3)—C(4) units are very similar, respectively, indicating that both positive and negative charge is extensively delocalized within the molecule. Similar differences were observed earlier by Simon and Sasvári between the structure of ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate and its hydrochloride salt [72AX(B)2405, 72CSC419].

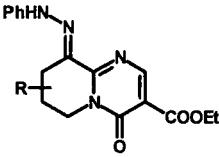


TABLE III  
 $^{15}\text{N}$  NMR DATA OF SOME 9-SUBSTITUTED TETRAHYDRO-4*H*-  
 PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES

	R	H	6-Me	7-Me	8-Me	Reference
	N(1)	-247.1	-251.6	-247.6	-248.5	85JCS(P2)1881
	N(5)	-231.5	-221.6	-231.8	-231.8	
	$^1J_{^{15}\text{N},\text{H}}$ , Hz	81.2	87.4	83.6	85.4	
	N(1)	-246.9	-247.7		-245.4	86JCS(P2)1911
	N(5)	-216.4	-201.9		-214.9	
	N(1)	-164.4	-164.2	-165.3	-163.7	83JCS(P2)1409
	N(5)	-214.8	-204.0	-215.9	-214.8	
	NMe <sub>2</sub>	-291.8	-291.9	-290.3	-292.9	
	N(1)		-160.8	-161.2	-161.0	83JCS(P2)1409
	N(5)		-199.1	-211.6	-211.6	
	NHPh		-253.2	-255.4	-254.9	
	N(1)		-161.1			83JCS(P2)1409
	N(5)		-199.1			
	NHPh		-264.5	-265.5		
	N(1)		-154.9	-155.7		83JCS(P2)1409
	N(5)		-194.7	-206.8		
	NHPh		-212.8	-214.6		
	$\equiv\text{N}-$		-28.0	-30.5		

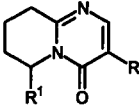
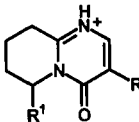
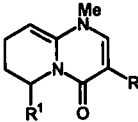
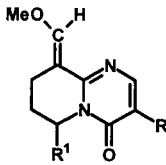
(continued)

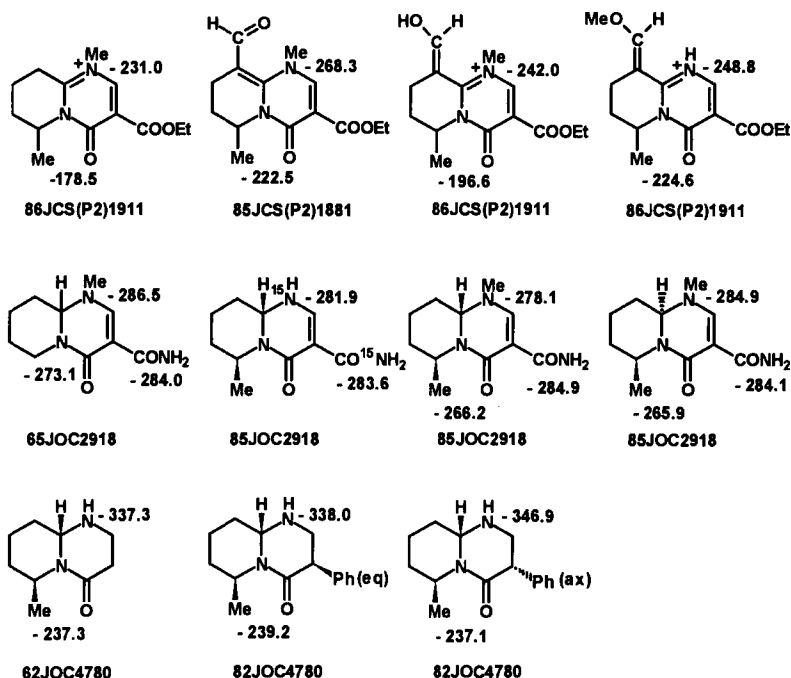
TABLE III (Continued)

	R	H	6-Me	7-Me	8-Me	Reference
	N(1)			-155.3		83JCS(P2)1409
	N(5)		-190.4	-206.0		
	NHPh		-225.7	-215.0		
	=N—			-29.6		

Introduction of a nitro group at C(3) of malonyl- $\alpha$ -aminopyridine **38** did not change the tautomeric form but did induce shortening of the C—O bonds and elongation of the adjacent C(2)—C(3) and C(3)—C(4) bonds [86AX(C)573]. In the ammonium salt of nitro derivative **39**, which does not contain a protonated N(1) atom, bond C(9a)—N(5) became elongated and bonds N(1)—C(9a) and C(4)—N(5) grew shorter [86AX(C)573]. However, if a carboxamido group is present at position 3 (compound **40**), the 2-hydroxy tautomer becomes predominant (93JHC33). In the unit cell there are two independent molecules. Both molecules contain strong intramolecular hydrogen bonds between the 2-hydroxy group and the amide oxygen atom and between the amide hydrogen and the 4-oxo group of the pyridopyrimidine ring.

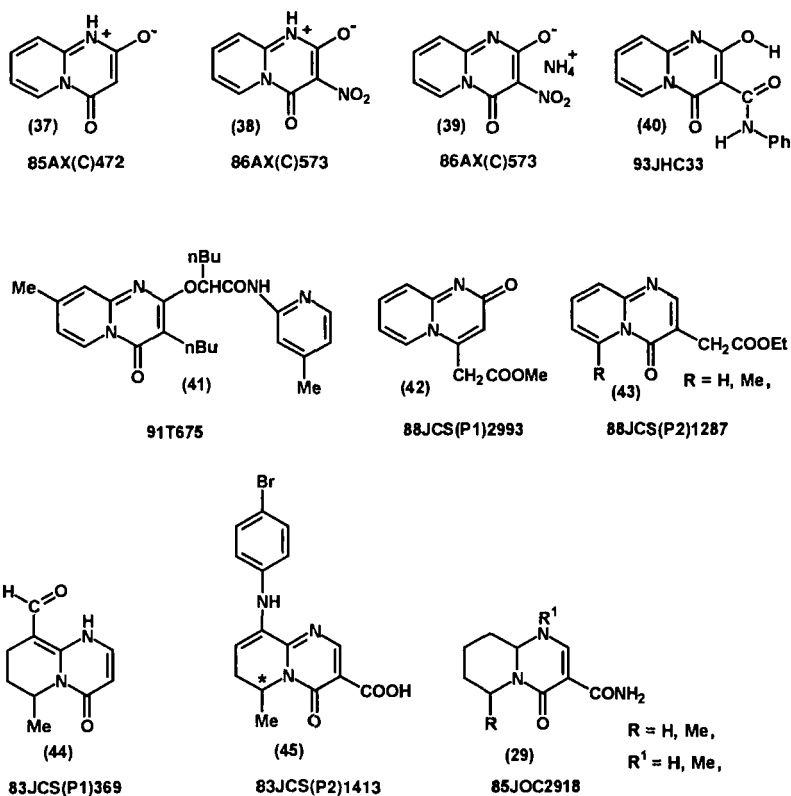
TABLE IV  
<sup>15</sup>N NMR DATA FOR SOME TETRAHYDRO-4*H*-PYRIDO  
 [1,2-*a*]PYRIMIDIN-4-ONES

					
R = COOEt	N(1)	-145.5	-229.7	-267.3	-161.8
R <sup>1</sup> = H	N(5)	-194.8	-187.8	-232.2	-204.6
R = COOEt	N(1)	-144.9	-222.8	-268.3	-161.2
R <sup>1</sup> = 6-Me	N(5)	-183.5	-177.9	-222.5	-193.5
R = CH <sub>2</sub> COOEt	N(1)	-143.5	-226.3		
R <sup>1</sup> = 6-Me	N(5)	-174.2	-168.8		



SCHEME 3.  $^{15}\text{N}$  NMR Data for some tetrahydro-, hexahydro-, and perhydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones

The ring transformation of 6-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones into 1,8-naphthyridines was earlier explained by the presence in the pyridopyrimidinone skeleton of a substituent at position 6 that caused the C(4)—N(5) bond to become longer [77JCS(P1)789]. The strain caused by the interaction between the neighboring 6-substituent and the 4-carbonyl group is relieved when the the C(4)—N(5) bond cleaves during the ring transformation. However, X-ray investigations of the 6-desmethyl- and 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetates **43** (R = H, Me) and -3-carboxylates **47** (R = H, Me, R<sup>1</sup> = COOEt) revealed that in the presence of the 6-methyl group the C(4)—N(5) bond is not elongated significantly, compared to that of the 6-desmethyl derivatives **43** (R = H) and **47** (R = H, R<sup>1</sup> = COOEt) (see Table V), but in the 6-methyl derivatives **43** (R = Me) and **47** (R = Me, R<sup>1</sup> = COOEt) the adjacent 6-methyl group and the oxygen atom of the 4-carbonyl group turn out of the plane of the bicycles in opposite directions [88JCS(P2)1287]. If the C(4)—N(5) bond is longer, then the dihedral angle between the methyl group and oxygen atom is smaller (see Table VI). It is interesting that deaza deriva-

SCHEME 4. X-Ray structure determination of some pyrido[1,2-*a*]pyrimidinones

tive **48** contains a similar C(4)—N(5) bond (88H385), as do the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **47** (R<sup>1</sup> = COOEt) (see Table VI).

Recently, the X-ray structures of ocaperidone **8** [92AX(C)1827], risperidone **7** [93AX(C)1698], and 4-methylene-3,4-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine **49** (90DOK619) were reported (see Table VII).

The fragmentation of 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate, -3-acetate, -3-propionate, and some methyl derivatives were studied by Erös-Takácsy *et al.* by mass spectrometry

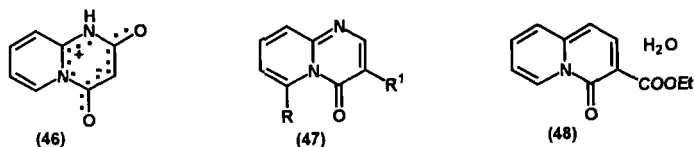


TABLE V  
BOND LENGTHS OF SOME UNSATURATED 2-Oxo-2*H*- AND 4-Oxo-4*H*-  
PYRIDO[1,2-*a*]PYRIMIDINES

Bond	Bond length (pm)							
	37 <sup>a</sup>	38 <sup>a</sup>	39 <sup>a</sup>	40A <sup>b</sup>	40B <sup>b</sup>	42	43 (R = H)	43 (R = Me)
N(1)—C(2)	139.5	138.7	138.0	130(2)	133(2)	136.2(3)	134.6(4)	134.5(3)
C(2)—C(3)	139.9	142.7	143.6	141(2)	140(2)	145.3(3)	136.2(5)	136.3(3)
C(3)—C(4)	138.7	141.1	140.7	135(2)	138(1)	133.9(3)	141.8(5)	141.3(3)
C(4)—N(5)	148.8	148.5	145.4	145(1)	145(1)	140.8(3)	143.4(4)	144.1(3)
N(5)—C(6)	137.5	137.9	139.1	139(1)	137(1)	138.7(3)	139.1(4)	140.7(4)
C(6)—C(7)	135.9	135.0	135.3	134(1)	137(2)	135.6(3)	134.4(5)	135.1(3)
C(7)—C(8)	140.7	140.5	140.7	145(2)	140(2)	141.3(4)	141.9(6)	140.1(3)
C(8)—C(9)	136.3	136.4	135.6	133(2)	132(2)	134.2(4)	135.7(5)	133.5(5)
C(9)—C(9a)	141.0	140.2	143.1	135(2)	143(2)	143.3(4)	142.1(5)	142.2(3)
N(1)—C(9a)	134.5	134.8	131.8	134(2)	133(1)	132.4(3)	132.7(4)	132.2(4)
N(5)—C(9a)	135.5	135.7	137.3	143(2)	138(1)	138.5(3)	139.1(4)	140.4(2)
C(4)—4-O	122.8	120.9	122.8	125(1)	125(1)		123.0(4)	122.5(2)
C(2)—2-O	125.1	123.6	124.5	135(2)	134(1)	124.7(3)		
C(4)—4-C						149.8(3)		
C(3)—3-C or 3-N				144(2)	148(2)		150.2(5)	150.2(3)

<sup>a</sup> The estimated standard deviation is 0.2 pm.

<sup>b</sup> Two crystallographically independent molecules (A and B) are present in the unit cell.

(89ACH333). The mode of fragmentation was found to be sensitive to the length of the alkyl chain connecting the ester group and the ring, and in some cases to the presence and position of a methyl group in the pyridine moiety.

The mass-spectral fragmentation of 4,6-dioxypyrido[1,2-*a*]pyrimidine-9-carboxylate **50** was studied (84AP873).

Laser microprobe mass analysis was used for the structural characterization of *N*-oxide metabolites of metrenperone (sinomedol **5**, R = Me), seganserine **6**, and ramastine **9** (88MI6). An assay of rimazolium **1** was developed by using an ion-selective electrode by direct titration with

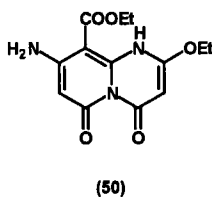
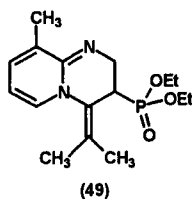


TABLE VI

SOME CHARACTERISTIC X-RAY DIFFRACTION DATA ON 4*H*-PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES (**43**, R = H, Me; **47**) AND 4*H*-QUINAZOLIN-4-ONE (**48**)

	Compound			Bond length C(4)—N(5) (pm)	Dihedral angle O=C(4)...C(6)—R (deg)	Reference
	R	R <sup>1</sup>				
<b>47</b>	Me <sup>a</sup>	COOEt	<b>A</b>	146.9	29	72AX(B)2405
			<b>B</b>	147.4	19	
<b>47</b>	Me	COOEt	HCl	151.5	12	72CSC419
<b>47</b>	H	COOEt		146.4		90UP
<b>48</b>			H <sub>2</sub> O	146.8	2.9	88H385
<b>43</b>	Me			144.2	40.4	88JCS(P2)1287
<b>43</b>	H			143.2	3	88JCS(P2)1287

<sup>a</sup> Two crystallographically independent molecules (**A** and **B**) are present in the unit cell.

TABLE VII

BOND LENGTHS OF THE PYRIDO[1,2-*a*]PYRIMIDIN-4-ONE MOIETY OF OCAPERIDONE (**8**), RISPERIDONE (**7**), AND 4-METHYLENE-3,4-DIHYDRO-2*H*-PYRIDO[1,2-*a*]PYRIMIDINE (**49**)

Bond	Bond length (pm)			
	8A <sup>a</sup>	8B <sup>a</sup>	7	49
N(1)—C(2)	135.9(8)	135.0(10)	137.2(6)	144.6(2)
C(2)—C(3)	136.5(9)	136.3(9)	135.7(7)	153.6(2)
C(3)—C(4)	140.0(10)	140.0(10)	143.5(5)	150.6(2)
C(4)—N(5)	144.4(9)	141.4(9)	139.5(6)	142.6(2)
N(5)—C(6)	138.6(9)	136.7(9)	148.8(5)	138.6(2)
C(6)—C(7)	134.0(20)	133.0(10)	150.5(9)	133.5(2)
C(7)—C(8)	139.0(20)	140.0(10)	146.0(9)	142.7(3)
C(8)—C(9)	136.2(9)	135.0(10)	146.8(7)	134.2(3)
C(9)—C(9a)	145.0(10)	145.0(10)	150.9(8)	146.2(2)
N(1)—C(9a)	131.2(8)	131.5(9)	130.9(5)	128.7(2)
N(5)—C(9a)	138.5(8)	138.1(8)	135.8(6)	140.5(2)
C(4)—4-O	120.7(9)	121.2(8)	123.4(6)	—
C(4)—4-C	—	—	—	133.0(2)
C(2)—2-C	150.0(10)	152.0(10)	150.4(6)	—
C(3)—3-C	151.0(10)	151.0(20)	151.2(6)	—
C(3)—3-P	—	—	—	179.9(1)
C(9)—9-C	148.4(9)	148.0(20)	—	148.7(4)

<sup>a</sup> Two crystallographically independent molecules (**A** and **B**) are present in the unit cell.

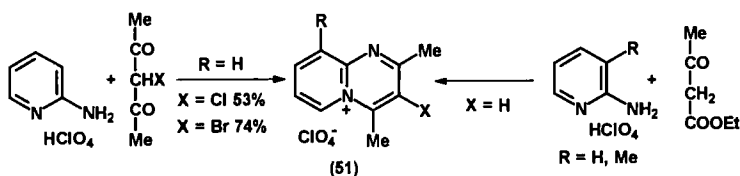
sodium tetraphenylborate (85MI18, 85MI23). Chinoin-127 (**19**) was determined both by cyclic voltammetry in sulfuric acid using Pt electrodes (84MI9, 84MI12) and by square wave polarography in aqueous potassium chloride using a Hg/Hg<sub>2</sub>SO<sub>4</sub> standard electrode (83MI13).

The coordination of 9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with Ni(II), Zn(II), Co(II), and Cd(II) ions was studied by potentiometric and polarographic methods. Stability constants of complexes were also determined (93MI25).

### III. Preparation of Pyrido[1,2-*a*]pyrimidines

#### A. PYRIDO[1,2-*a*]PYRIMIDINIUM SALTS

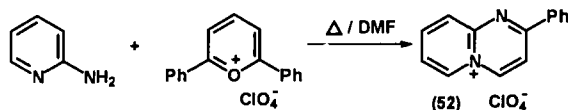
The cyclocondensation of 2-aminopyridinium perchlorate and 3-haloacetylacetones in ethanol at 120–130°C gave 3-halo-2,4-dimethylpyrido[1,2-*a*]pyrimidinium perchlorate **51** (R = Cl, Br) (90ZAK502; 91KGS1381). Cyclocondensation of 2-aminopyridinium perchlorate and



acetylacetone at 160°C gave 2,4-dimethylpyrido[1,2-*a*]pyrimidinium perchlorate (91KGS1381).

Gashev *et al.* observed an unusual reaction when 1.5–5-fold excesses of ethyl acetoacetate were reacted with 2-aminopyridinium perchlorates at 120–170°C. Instead of 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, 2,4-dimethylpyrido[1,2-*a*]pyrimidinium perchlorates **51** (*R* = H; 9-OH; *X* = H) were obtained (88KGS1288; 91KGS1381).

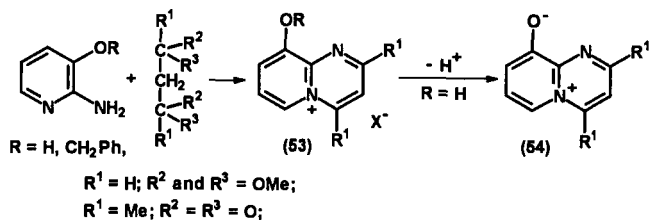
2-Phenylpyrido[1,2-*a*]pyrimidinium perchlorate **52** was obtained in 12% yield when 2-aminopyridine was reacted with 2,6-diphenylpyrylium perchlorate (83KGS893).



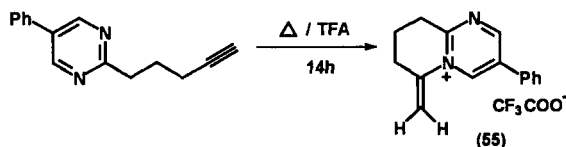
Reaction of 2-amino-3-hydroxypyridine with 1,1,3,3-tetramethoxypropane and acetylacetone in a mixture of methanol and 65% aqueous perchloric acid at 50°C gave 9-hydroxypyridopyrimidinium perchlorates **53** (*R* = H, *R*<sup>1</sup> = H, Me) in good yields, respectively (91TL4307). 9-Hydroxypyrido[1,2-*a*]pyrimidinium perchlorate **53** (*R* = *R*<sup>1</sup> = H, *X* = ClO<sub>4</sub><sup>-</sup>) was also prepared when 2-amino-3-hydroxypyridinium perchlorate was reacted with tetraethoxypropane in boiling ethanol (91KGS1381).

Under similar conditions 2-amino-3-benzyloxy pyridine gave a mixture of 9-benzyloxy- **53** (*R* = CH<sub>2</sub>Ph; *R*<sup>1</sup> = H, Me) and 9-hydroxypyridopyrimidinium perchlorates **53** (*R* = H; *R*<sup>1</sup> = H, Me). When the latter reactions were carried out at room temperature for 72 hours, 9-benzyloxy derivatives **53** (*R* = CH<sub>2</sub>Ph; *R*<sup>1</sup> = H, Me) were obtained in moderate yields. The perchlorate anion was changed to bromine in water with potassium bromide. When the aqueous solutions of pyridopyrimidinium salts **53** (*R* = H; *R*<sup>1</sup> = H, Me; *X* = Br, ClO<sub>4</sub>) were treated with IRA 4015 or Dower 50W ion-exchange resin, the betaine products **54** were isolated by evaporation of the aqueous reaction mixtures to dryness, and their structures were characterized by <sup>1</sup>H and <sup>13</sup>C NMR (91KGS1381, 91TL4307).



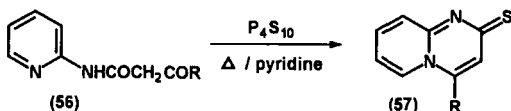


The intramolecular coplanar cycloamination reaction of 2-(4-pentynyl)-5-phenylpyrimidine afforded 6-methylene-3-phenyl-6,7,8,9-tetrahydropyr-ido[1,2-*a*]pyrimidinium trifluoroacetate **55**, which could not be isolated in pure form (90T595).



### B. 2-Oxo-2*H*-PYRIDO[1,2-*a*]PYRIMIDINES

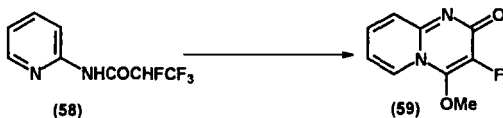
The treatment of *N*-(2-pyridinyl)acylacetamides **56** with  $\text{P}_4\text{S}_{10}$  gave 4-substituted 2*H*-pyrido[1,2-*a*]pyrimidine-2-thiones **57** in 28% yield [88JCS(D)433].



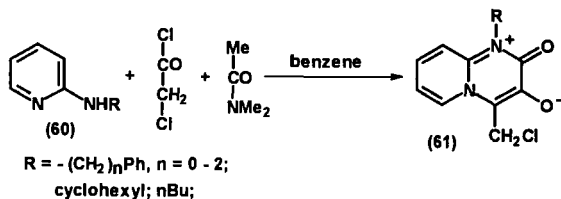
Heating *N*-(2-pyridyl)-2,3,3,3-tetrafluoropropionamide **58** in boiling methanol in the presence of sodium methoxide afforded 3-fluoro-4-methoxy-2*H*-pyrido[1,2-*a*]pyrimidin-2-one **59** in 14% yield (88ZOR1082).

The reaction of 2-(substituted amino)pyridines **60** and a mixture of chloroacetyl chloride and *N,N*-dimethylacetamide for 1 hour at 50°C gave zwitterionic 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **61** (89CCC1376; 91MI1).

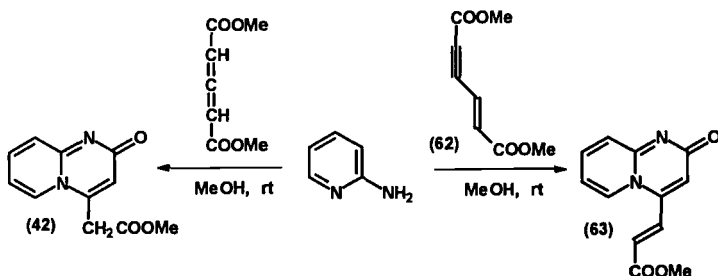
Methyl 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine-4-acetate **42** was prepared in



the reaction of 2-aminopyridine and dimethyl penta-2,3-dienedioate under argon [88JCS(P1)2993].

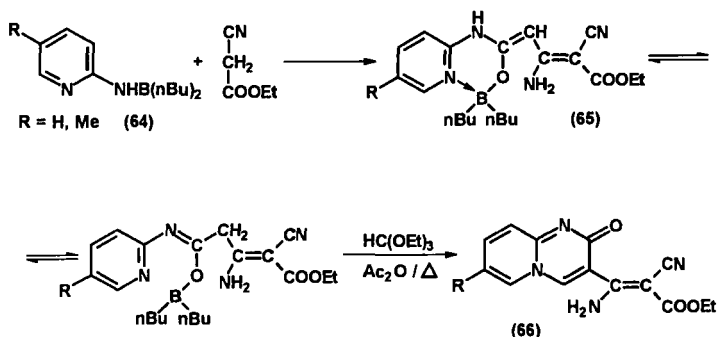


When dimethyl hex-2-en-4-yne-1,6-dioate **62**, a dimerized product of methyl propiolate, was reacted with 2-aminopyridine in refluxing methanol for 44 hours (*E*)-3-(2-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-4-yl)prop-2-enoate **63** was obtained, but the product could not be purified either by chromatography or by recrystallization [82JCS(P1)1905].

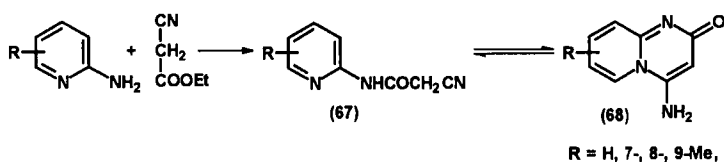


The condensation of 2-aminopyridine derivatives **64** with ethyl cyanoacetate gave amides **65**, which were cyclized to 2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **66** by the treatment of triethyl orthoformate and acetic anhydride (90IZV229).

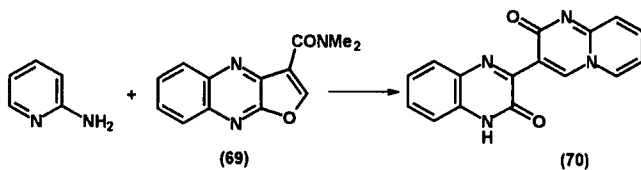
When 2-aminopyridines were reacted with ethyl cyanoacetate in ben-



zene at 80°C under 14 kbar pressure for 5 hours, 4-amino-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **68** were obtained in 40–65% yields (89IZV211; 90IZV2107). The use of diethyl ether or acetonitrile instead of benzene was unsuccessful. At 14 kbar benzene is present as a solid, and the cyclocondensation occurs in the micropores of solid benzene. Heating pyrido[1,2-*a*]pyrimidin-2-ones **68** at 150–180°C and 1 mm Hg resulted in the formation of ring-opened products **67**. Ring-opened products **67** were also formed in a dimethylformamide solution of **68** at ambient temperature for 5–6 weeks. The 2-acylamidopyridines **67** also could be cyclized to pyrido[1,2-*a*]pyrimidin-2-ones **68** by heating in pyridine or in triethylamine.

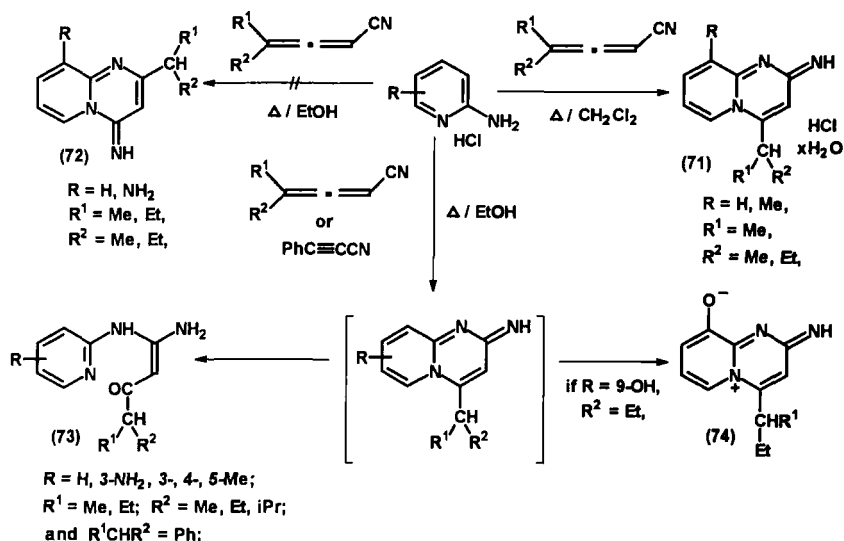


Reaction of 2-aminopyridine and 3-(*N,N*-dimethylaminocarbonyl)furo[2,3-*b*]quinoxaline **69** in boiling butanol gave 2-(2-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-3,4-dihydroquinoxalin-2-one **70** (80CPB3537).



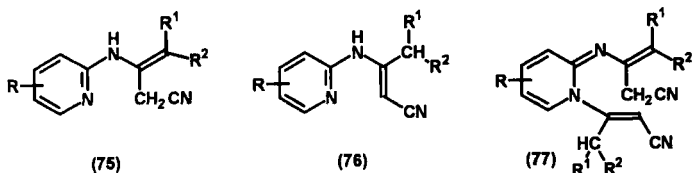
Landor and his colleagues studied the reaction of 2-aminopyridines with allenic nitriles and phenylpropynenitrile [81TL4127; 88JCS(P1)975].

The reaction of 2-aminopyridine hydrochlorides and allenic nitriles either neat at 90°C for 20 hours or in boiling methylene chloride for 15 hours afforded unstable 2-imino-2*H*-pyrido[1,2-*a*]pyrimidine hydrochlorides **71**, which could be isolated as hydrates in about 50% yield [88JCS(P1)975]. If the reactions were carried out in boiling 95% ethanol for 72 hours, the initially formed 2-imino-2*H*-pyrido[1,2-*a*]pyrimidines **71** were hydrolyzed and 2-pyridyl ketones **73** could be isolated. Under the latter conditions 3-hydroxy-2-aminopyridine gave 2-iminopyridopyrimidines **74**, which were stabilized by the formation of zwitterionic structures (Scheme 5). [Earlier the ring-opened products **73** (R = H, 3-NH<sub>2</sub>) were described as a 4-imino-4*H*-pyrido[1,2-*a*]pyrimidine derivative **72** (81TL4127)].



SCHEME 5

The reaction of allenic nitrile and 2-amino-6-methyl- and -4,6-dimethylpyridine gave a mixture of mono- and bis-adducts tentatively formulated as **75**, **76**, and **77** [88JCS(P1)975], while 2-amino-3-nitro-, 2,6-diamino-, and 2-amino-3,5-dibromopyridines do not react even after refluxing for 120 hours.

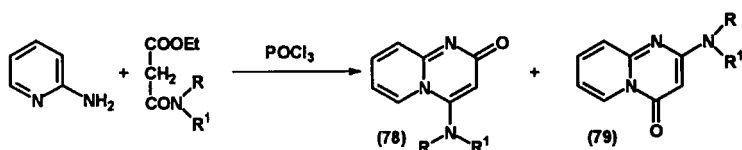


2-Aminopyridines and phenylpropynenitrile also gave ring-opened 2-pyridyl ketones **73** ( $-\text{CHR}^1\text{R}^2 = \text{Ph}$ ) via 2-iminopyrido[1,2-*a*]pyrimidines in boiling ethanol [88JCS(1)975].

### C. 2-Oxo-2*H*- AND 4-Oxo-4*H*-PYRIDO[1,2-*a*]PYRIMIDINES

In some reactions the isomeric 2-oxo-2*H*- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines are simultaneously formed (82FES747, 82JHC909, 82MI4, 82UPI; 87JHC329; 88FES705; 92HCA1262).

Reaction of 2-aminopyridines and *N,N*-disubstituted malonamates afforded mixtures of 4-amino-2-oxo-2*H*- and 2-amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines **78** and **79** in boiling 1,2-dichloroethane with phosphoryl chloride (82FES747; 87JHC329; 88FES705). Generally the ratio of the 2-oxo and 4-oxo isomers **78** and **79** increased in the presence of bulkier R and/or R<sup>1</sup> groups (see Table VIII).

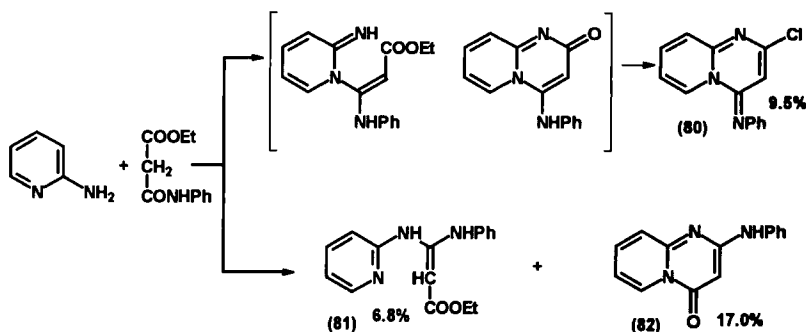


Besides bicyclic products **80** and **82**, a condensation product **81** was also isolated from the reaction mixture in the case of *N*-phenylmalonamate (87JHC329).

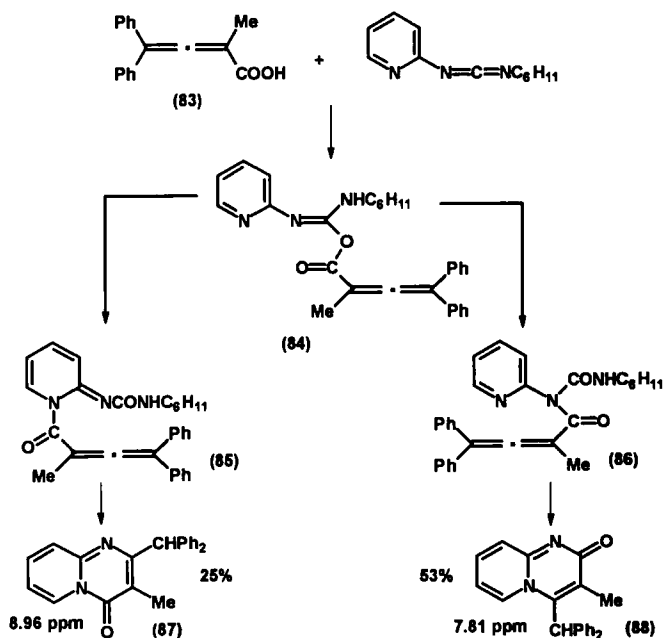
The reaction of *N*-cyclohexyl-*N*-(2-pyridyl)carbodiimide and the allenic acid **83** in dry tetrahydrofuran at ambient temperature for 3 days afforded a 2 : 1 mixture of isomeric 2-oxo-2*H*- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines **88** and **87** instead of the expected Diels–Alder adduct (92HCA1262). The formation of an activated ester **84** was suggested in the first step, which underwent a 1,5- or 1,3-acyl migration, giving rise to the isomeric pyrido[1,2-*a*]pyrimidines **87** and **88** via acylureas **85** and **86**, respectively (Scheme 6).

TABLE VIII  
PRODUCTS **78** AND **79** IN THE REACTION OF 2-AMINOPYRIDINES AND  
*N,N*-DISUBSTITUTED MALONAMATES

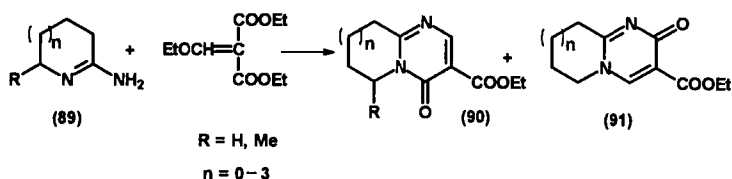
R	R <sup>1</sup>	2-Oxo isomer <b>78</b> (%)	4-Oxo isomer <b>79</b> (%)	Reference
Me	Me	10.3	7.6	82FES747
Me	Et	15.8	5.5	82FES747
Et	Et	47.3	4.1	82FES747
<i>n</i> Pr	<i>n</i> Pr	49.7	4.8	82FES747
<i>i</i> Pr	<i>i</i> Pr	42.4	9.4	82FES747
<i>n</i> Bu	<i>n</i> Bu	50.4	5.0	88FES705
	—(CH <sub>2</sub> ) <sub>4</sub> —	31.9	1.1	82FES747
	—(CH <sub>2</sub> ) <sub>5</sub> —	23.6	4.4	88FES705
	—CH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub> —	15.8	18.2	82FES747
Me	Ph	25.0	20.0	87JHC329
Et	Ph	35.0	10.4	87JHC329
<i>n</i> Bu	Ph	29.4	13.0	88FES705
Et	CH <sub>2</sub> Ph	48.3	5.2	88FES705



The cyclocondensation of the amidines **89** ( $n = 0-3$ ) and diethyl ethoxy-methylenemalonate afforded an isomeric mixture of 4-oxo- and 2-oxo bicycles **90** and **91** in ethanol at  $-10^{\circ}\text{C}$  and  $0^{\circ}\text{C}$  (82JHC909, 82MI4). The yield of 2-oxo isomer decreased with increasing ring size ( $n$ ). 4-Oxo-4*H*-tetrahydropyridopyrimidine **90** ( $n = 1$ ,  $R = \text{H}$ ) was obtained in 72% yield, and its 2-oxo isomer **91** ( $n = 1$ ,  $R = \text{H}$ ) in 25% yield. If a methyl group was present, only the 4-oxo isomer **90** ( $n = 1$ ,  $R = \text{Me}$ ) was formed from



SCHEME 6



the amidine **89** ( $n = 1$ ,  $\text{R} = \text{Me}$ ). A mixture of the appropriate 2-oxo-2*H*- and 4-oxo-4*H*-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidines was also obtained in the reaction of 2-amino-3,4,5,6-tetrahydropyridine **89** ( $n = 1$ ,  $\text{R} = \text{H}$ ) and  $\beta$ -oxo esters (82UP1).

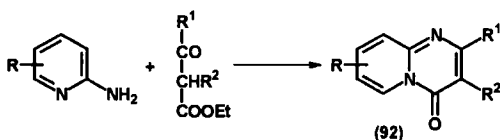
#### D. 4-Oxo-4*H*-PYRIDO[1,2-*a*]PYRIMIDINES

##### 1. From $\beta$ -Oxo Esters and Their Congeners

Reaction of 2-aminopyridines and  $\beta$ -oxo esters under acidic conditions [most frequently by heating in polyphosphoric acid (e.g., 81USP4291036; 82MI6; 83JHC1053; 88GEP3644825; 90JHC881; 91MIP2) or in a mixture of phosphoryl chloride–polyphosphoric acid (e.g., 81USP4291036; 82MI6; 84S152)] afforded 2-substituted or 2,3-disubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **92**.

Cyclocondensation does not proceed in phosphoryl chloride alone, but it happens smoothly if somewhat more than a catalytic amount of polyphosphoric acid is added to phosphoryl chloride (84S152). Phosphoryl chloride acts both as a solvent and as an alcohol and water scavenger. Thus the work-up procedure is more comfortable because when the evolution of hydrogen chloride ceases, the excess phosphoryl chloride is reacted with ethanol, and the hydrogen chloride of the pyrido[1,2-*a*]pyrimidinone is precipitated from the alcoholic reaction mixture during cooling (84S152). Sometimes the excess phosphoryl chloride can be decreased by applying a further cosolvent (e.g., xylene) (86MIP1).

2-Amino-6-hydroxypyridine and ethyl acetoacetate were unsuccessfully reacted in a mixture of phosphoryl chloride–polyphosphoric acid. Ethyl 2-aminopyridine-3-carboxylate gave 2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]

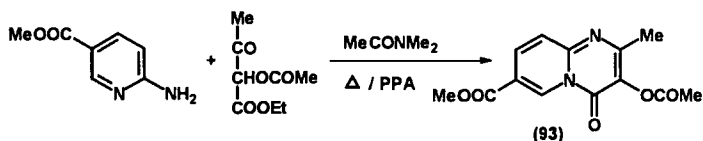


pyrimidine-9-carboxylic acid **92** ( $R = 9\text{-COOH}$ ,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) in 5% yield (84S152).

2-Aminopyridine and its 3-hydroxy and 6-methyl derivatives were reacted with ethyl 2-chloro- and 2-phenoxyacetoacetates by heating in a mixture of phosphoryl chloride–polyphosphoric acid to give the appropriate 3-substituted 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (83H1083).

In polyphosphoric acid 2-aminopyridines were successfully reacted with ethyl acetoacetate [82JHC1017; 83JHC1053; 83MI12; 87EUP218423; 90JHC881; 92MI17, 92MIP4; 93IJC(B)978, 93MIP2], its 4-chloro (83EUP81945, 83JHC1053; 90JHC881), 2-chloro- (92MI16) and 2-alkyl derivatives (83MI12, 83PHA218; 88GEP3644825; 90JHC881), ethyl aroylacetates (83JHC1053; 86EUP168262; 90JHC881; 92MI16) and other aroylacetates (83JHC1053; 86EUP168262; 90JHC881; 92MI16), and ethyl alkanoylacetates (83JHC1053; 88GEP3644825).

Only resinous products and methyl 6-acetamidopyridine-3-carboxylate were obtained when methyl 6-aminopyridine-3-carboxylate was reacted with ethyl 2-acetoxyacetoacetate by heating in phosphorus pentoxide, methanesulfonic acid, or polyphosphoric acid in the absence or presence of a solvent such as toluene, xylene, or methylene chloride. However the desired methyl 3-acetoxy-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate **93** was obtained when the above components were reacted in *N,N*-dimethylacetamide in the presence of polyphosphoric acid at 100°C for 48 hours (84FES837).



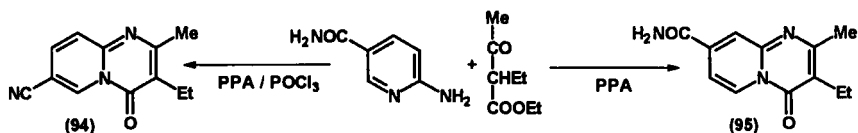
The reaction of 2-amino-4-methylpyridine and dimethyl 1,3-acetonedicarboxylate in polyphosphoric acid afforded 2,8-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one instead of the expected methyl 8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-acetate (83JHC1053).

The cyclocondensation of 2-amino-6-methylpyridine and diethyl 3-oxopimelate did not occur at room temperature by standing over concentrated sulfuric acid; instead, it gave ethyl 4-(6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)butanoate by heating in polyphosphoric acid in 25% yield (87SC319).

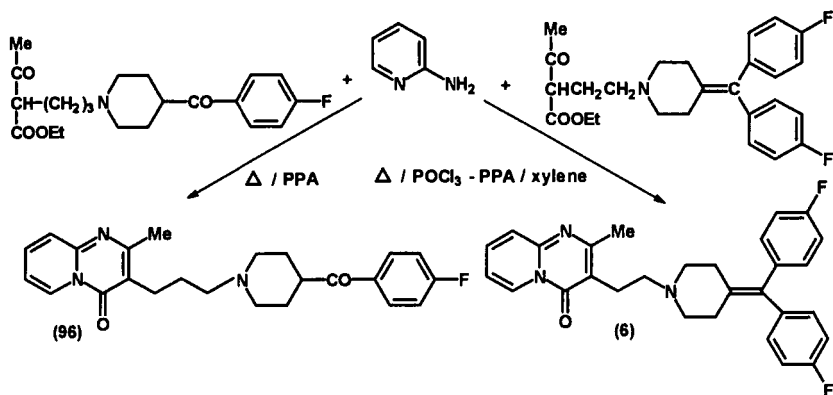
When 6-aminopyridine-3-carboxamide was reacted with ethyl 2-ethylacetoacetate in a mixture of phosphoryl chloride–polyphosphoric acid, 7-cyano-3-ethyl-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **94** was obtained



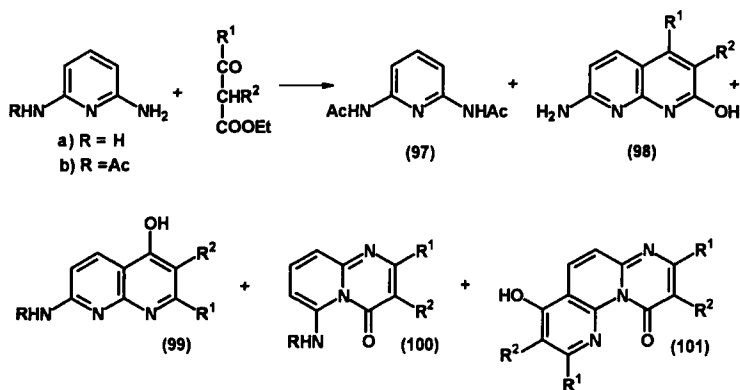
(83PHA218). In polyphosphoric acid, 3-ethyl-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxamide **95** was the product.



The 3-propylidene homolog of pirenperone **96** and seganserin **6** were prepared when 2-aminopyridine reacted with the appropriate ethyl 2-substituted acetoacetate by heating in polyphosphoric acid (81EUP37265; 82USP4342870) and in a mixture of phosphoryl chloride–polyphosphoric acid (86MIP1), respectively.



Ferrarini *et al.* studied the reaction of 2,6-diamino- and 2-amino-6-acetamidopyridine with different  $\beta$ -oxo esters in polyphosphoric acid at 80°C (90JHC881). Generally, complex reaction mixtures that contained different bi- and tricyclic products were obtained (see Scheme 7 and Table IX). The products were separated by flash chromatography. In the case of 2-amino-6-acetamidopyridine, the 2,6-diacetamidopyridine **97** was the main product. This compound **97** was also obtained by transamidation in good yield when 2-amino-6-acetamidopyridine was heated in polyphosphoric acid at 80°C. 2-Hydroxy-1,8-naphthyridines **98** were formed in a Conrad–Limpach-type cyclocondensation of 2-aminopyridines and  $\beta$ -keto ester, while 4-hydroxy-1,8-naphthyridines **99** were probably formed by a ring transformation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **100** obtained by the cyclocondensation of 2-aminopyridines and a  $\beta$ -keto ester. The cyclocondensation of 7-amino-4-hydroxy-1,8-naphthyridine **99** (R = H) and a



SCHEME 7

second mole of  $\beta$ -oxo ester gave the tricyclic pyrido[1,2-*a*][1,8]naphthyridine **101**. In the reaction of 2,6-diaminopyridine and ethyl 4,4,4-trifluoroacetoacetate, only 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **100** ( $\text{R} = \text{R}^2 = \text{H}$ ,  $\text{R}^1 = \text{CF}_3$ ) was obtained.

Methyl 2-methyl-3-propyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate was obtained in the reaction of methyl 6-aminopyridine-3-carboxyl-

TABLE IX  
PRODUCTS IN THE REACTION OF AMINOPYRIDINES AND  $\beta$ -OXO ESTERS IN  
POLYPHOSPHORIC ACID (90JHC881) (SCHEME 7)

Starting 2-amino pyridine R	$\beta$ -Oxo ester		Products (%)				
	R <sup>1</sup>	R <sup>2</sup>	97 <sup>a</sup>	98	99	100	101 <sup>b</sup>
H	Me	H		3	51	12	27
H	CH <sub>2</sub> Cl	H		50		9	
H	CF <sub>3</sub>	H				78	
H	Me	Me			41	7	16
H	<i>n</i> Pr	H		5	41	10	22
H	Ph	H		16	15	4	4
Ac	Me	H	68			5 + 4 <sup>c</sup>	50
Ac	CH <sub>2</sub> Cl	H	47	2		6 + 6 <sup>c</sup>	42
Ac	CF <sub>3</sub>	H	37	4		39 <sup>c</sup>	
Ac	Me	Me	73			2 + 8 <sup>c</sup>	68
Ac	<i>n</i> Pr	H	50		5 <sup>c</sup>	12 + 9 <sup>c</sup>	45
Ac	Ph	H	41		22 + 15 <sup>c</sup>	2 + 5 <sup>c</sup>	

<sup>a</sup> Yields calculated on the theoretically formed 2,6-diacetamidopyridine.

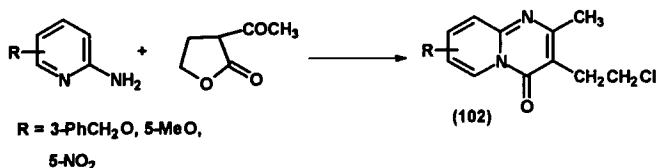
<sup>b</sup> Yields calculated on the  $\beta$ -keto ester.

<sup>c</sup> R = H.

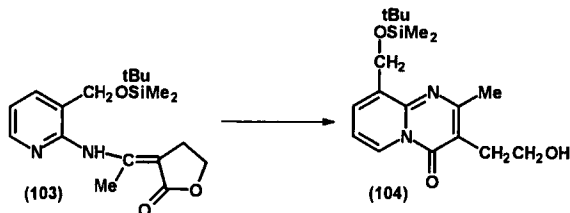
ate and ethyl 2-propylacetoacetate in the presence of *p*-toluene sulfonic acid at 140°C for 60 hours (83MI12).

4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones were also obtained when a hydrohalide salt of 2-aminopyridine reacted with  $\beta$ -oxo ester in heated pyridine (81USP4291036).

The reaction of 3-benzyloxy-, 5-methoxy-, and 5-nitro-2-aminopyridines and 3-acetyl-4,5-dihydro-2(3*H*)-furanone in warm toluene in the presence of phosphoryl chloride afforded 3-(2-chloroethyl)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **102** (84EUP110435; 90EUP368388; 92USP5158952).



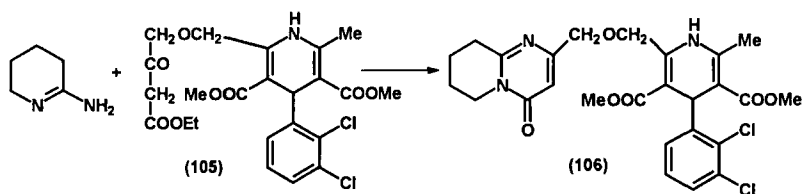
3-(2-Hydroxyethyl)pyrido[1,2-*a*]pyrimidin-4-one **104** was prepared by the ring closure of 2(3*H*)-furanone **103** in 1,2-dichloroethane in the presence of aluminum trichloride at 80°C for 0.5 hour in 54% yield after column chromatography (91EUP453042).



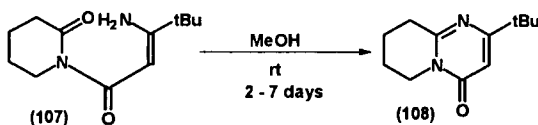
2-Amino-3,4,5,6-tetrahydropyridines were usually reacted with  $\beta$ -oxo esters in the absence or presence of a base to give 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [83JHC393; 85EUP132375, 85JOC166; 88JCS(P1)2653]. In these cases the formation of the isomeric 6,7,8,9-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one must also be considered (see Section II, C).

The cyclocondensation of  $\beta$ -oxo ester **105** and 2-aminotetrahydropyridine in refluxing ethanol in the presence of DBU yielded tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **106** (85EUP132375).

2-Methyl-7-phenyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared in the reaction of 2-amino-5-phenyl-3,4,5,6-tetrahydropyridine and ethyl acetoacetate either in refluxing xylene or in boiling alcoholic sodium ethylate (83JHC393).

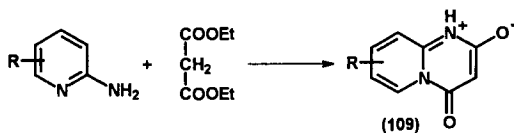


Reaction of  $\delta$ -valerolactam and ethyl 3-aminocrotonate in boiling phosphoryl chloride gave 2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (91KPS394). 2-*tert*-Butyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **108** was formed when piperidino derivative **107** was allowed to stand in methanol (85JOC166, 85TL3247).



## 2. From Malonic Esters and Their Congeners

“Malonyl- $\alpha$ -aminopyridine” **37** was prepared in 45% yield when malonic acid was reacted with 2-aminopyridine in boiling pyridine in the presence of mole equivalents of benzenesulfonyl chloride for 15 minutes (83MI19). “Malonyl- $\alpha$ -aminopyridine” **37** was also obtained in the reactions of 2-aminopyridine and excess diethyl malonate by heating in the absence of a solvent. 9-Methyl-, 9-chloro-, and 7-methyl derivatives **109** (R = 9-Me, 9-Cl, 7-Me) were prepared from the appropriate 2-aminopyridine and diethyl malonate in boiling xylene in 20–53% yields (90ZC98).

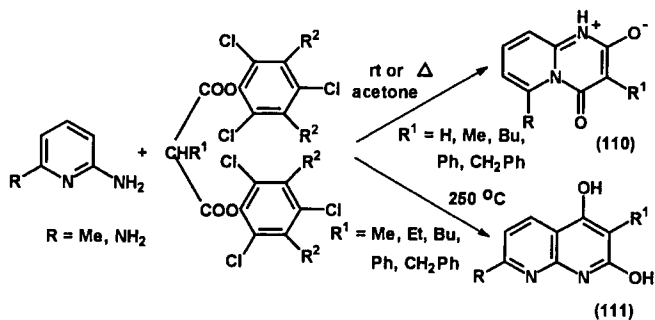


3-Butyl- and 3-(3-methyl-2-butenyl)-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were prepared in the reaction of 2-aminopyridine and diethyl 2-butyl- and 2-(3-methyl-2-butenyl)malonates, respectively (84MI-14; 89MI16).

2-Hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were prepared from 2-aminopyridines with diethyl [4-(2-cyanophenyl)phenyl]methylmalonate at 180°C (94MI2).

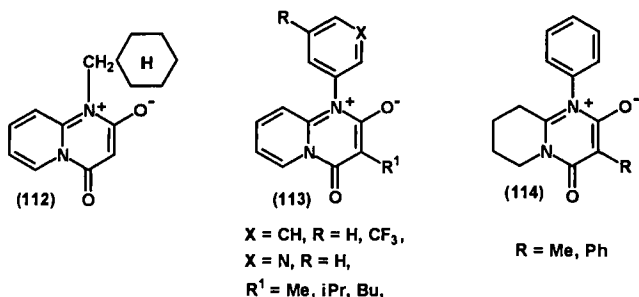
Reactions of 2-amino-6-methyl- and 2,6-diaminopyridine with different esters of malonic acid were investigated by Schober and Kappe (88JHC1231) (Scheme 8). A solution of 2-amino-6-methylpyridine and bis(2,4,6-trichlorophenyl) or bis(pentachlorophenyl) malonates in acetone in the presence of two equivalents of triethylamine at ambient temperature gave 3-substituted 6-methylpyridopyrimidines **110** ( $R = \text{Me}$ ,  $R^1 \neq \text{H}$ ) in 39–47% yield. When bis(2,4,6-trichlorophenyl) malonates ( $R^1 = \text{Ph}$ ,  $\text{CH}_2\text{Ph}$ ,  $R^2 = \text{H}$ ) were reacted with 2-amino-6-methylpyridine in refluxing acetone in the absence of triethylamine, the appropriate pyrido[1,2-*a*]pyrimidine **110** ( $R = \text{Me}$ ;  $R^1 = \text{Ph}$ ,  $\text{CH}_2\text{Ph}$ ) was obtained in 63–70% yield. The application of bis(2,4,6-trichlorophenyl) malonates was advantageous because of the greater solubility of 2,4,6-trichlorophenol in acetone, and this ester gave purer crude products. 2,6-Diaminopyridine was reacted with bis(2,4,6-trichlorophenyl) 2-substituted malonates in acetone in the absence of triethylamine at room temperature for 30 minutes to afford 3-substituted 6-aminopyrido[1,2-*a*]pyrimidines **110** ( $R = \text{NH}_2$ ,  $R^1 \neq \text{H}$ ). If 2-amino-6-methyl- and 2,6-diaminopyridines were reacted with bis(2,4,6-trichlorophenyl) malonate and diethyl malonate at 250°C in the absence of solvent for 30 minutes or in refluxing diphenyl ether for 0.5–2 hours, the products were 1,8-naphthyridines **111** (see also Section III,C). Bis(2,4,6-trichlorophenyl) malonate was reacted with 2-amino-6-methyl- and 2,6-diaminopyridine in refluxing acetone to give 3-unsubstituted 6-methyl- and 6-aminopyrido[1,2-*a*]pyrimidines **110** ( $R = \text{Me}$ ,  $\text{NH}_2$ ;  $R^1 = \text{H}$ ) in poor and 79% yields, respectively.

Different malonyl- $\alpha$ -aminopyridines **110** ( $R = \text{H}$ ,  $\text{Me}$ ) were prepared from 2-aminopyridine and its methyl-substituted derivatives with diethyl 2-substituted malonates at 160–180°C with continuous distillation of the ethanol formed, or with bis(2,4,6-trichlorophenyl) 2-substituted malonates in acetone under reflux, or at ambient temperature in the presence of triethylamine (91T675).

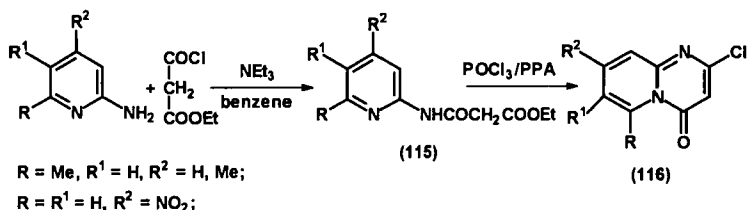


SCHEME 8

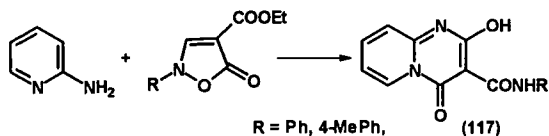
Bis(2,4,6-trichlorophenyl) malonate reacted smoothly with 2-[(cyclohexylmethyl)amino]pyridine at 160–175°C under nitrogen to yield pyrido[1,2-*a*]pyrimidinone **112** (81JMC1284). Reaction of an equimolar mixture of bis(2,4,6-trichlorophenyl) 2-substituted malonates and 2-(phenylamino)-, 2-(3-pyridylamino)-, and 2-(3-trifluorophenyl)amino]pyridines at 160–180°C gave cardiotonic mesoionic pyrido[1,2-*a*]pyrimidinones **113** (91AP863). Mesoionic tetrahydropyridopyrimidinones **114** were obtained in the reaction of 2-(phenylamino)-3,4,5,6-tetrahydropyridine and bis(2,4,6-trichlorophenyl) 2-substituted malonates (85CB4567; 86CC687).



*N*-(2-Pyridyl)malonamates **115**, obtained in the reaction of 2-aminopyridines and malonic acid half-ester chloride, were cyclized in a mixture of phosphoryl chloride–polyphosphoric acid at 130°C for 2–5.5 hours to give 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **116** (84S152).



Heating a mixture of 2-aminopyridine and ethyl 2,5-dihydro-5-oxo-2-arylisoazole-4-carboxylates at 200°C for 2 minutes gave 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides **117** in 35–37% yields (93JHC33).



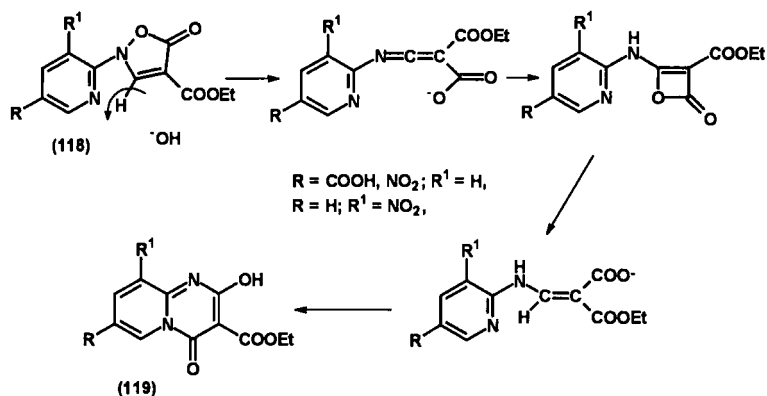
The rearrangement of ethyl 2-(5-carboxy-2-pyridyl)-5-oxo-2,5-dihydro-isoxazole-4-carboxylate **118** ( $R = \text{COOH}$ ,  $R^1 = \text{H}$ ) by the action of 2.5 *M* aqueous sodium hydroxide at 40°C for 10 minutes and in tetrahydrofuran by the action of saturated aqueous sodium carbonate solution at ambient temperature for 5 hours yielded pyrido[1,2-*a*]pyrimidine derivative **119** ( $R = \text{COOH}$ ,  $R^1 = \text{H}$ ). The proposed reaction mechanism is depicted in Scheme 9 (89AJC2161).

This reaction was extended to prepare 7-nitro- and 9-nitro derivatives of pyrido[1,2-*a*]pyrimidinone **119** ( $R = \text{NO}_2$ ,  $R^1 = \text{H}$ ;  $R = \text{H}$ ,  $R^1 = \text{NO}_2$ ) when the appropriate starting material **118** was heated in boiling dichloromethane in the presence of triethylamine or when it was stirred in aqueous sodium hydroxide at 20°C (92AJC1825) or treated with sodium azide in aqueous tetrahydrofuran (92AJC2037). Semiempirical molecular orbital calculations (AM1) indicated that the 2-hydroxy-4-oxo tautomeric forms **119** are more stable than the alternative 4-hydroxy-2-oxo tautomeric forms.

3-Substituted 2-mercapto-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **121** were prepared by the cyclization of thioamides **120**, prepared from 2-pyridyl-isothiocyanate and the appropriate CH acids, in boiling ethanol by the action of sodium ethylate (81CCC2428).

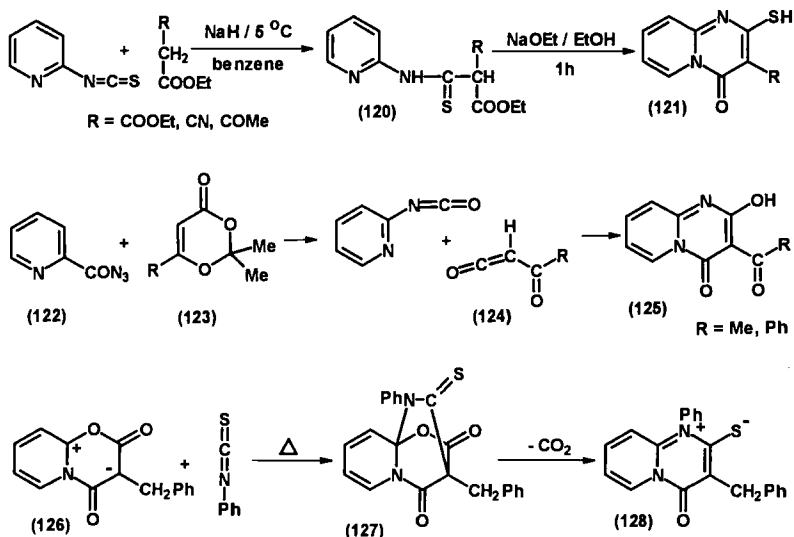
Sato *et al.* prepared pyrido[1,2-*a*]pyrimidines **125** by [2+4]cycloaddition reactions starting from 2,2-dimethyl-1,3-dioxin-4-ones **123** and 2-picolinoyl azide **122**. Heating compounds **122** and **123** in xylene at 120°C for 30 minutes gave acylketenes **124** and 2-pyridyl isocyanate, which yielded pyrido[1,2-*a*]pyrimidines **125** in a [2+4]cycloaddition (84CPB2602).

3-Benzyl-1-phenylpyrido[1,2-*a*]pyrimidine derivative **128** was obtained in 2.5% yield in the reaction of mesoionic 6-oxo-6*H*-1,3-oxazin-3-ium-4-



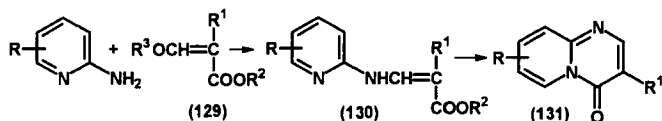
SCHEME 9

olate **126** and phenyl isothiocyanate at 100°C for 220 hours via a [2+4]cycloadduct **127** [82ZN(B)222].



### 3. From 2-Alkoxymethylenemalonates, 3-Alkoxyacrylates, and Their Congeners

In this type of synthesis 2-aminopyridines are usually reacted with 2-alkoxymethylenemalonates **129** ( $\text{R}^1 = \text{COOR}^2$ ) or 3-alkoxyacrylates and 2-formylalkanoates **129** ( $\text{R}^1 = \text{CHO}$ ), then the condensation products **130** are thermally cyclized in the next step (e.g., 85JHC481) or under acidic conditions [e.g., 84S152; 92MI17; 93IJC(B)978] to give 3-substituted 4H-pyrido[1,2-*a*]pyrimidin-4-ones **131**. Cyclization under basic conditions is reversible and results in an equilibrium mixture of 2-pyridyl amine derivative **130** and bicyclic **131** [e.g., 84JCS(P1)1799].

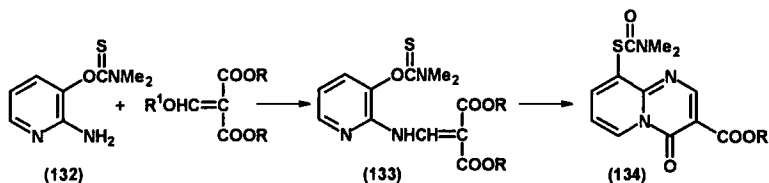


Thermal cyclization of 3-benzyloxy (89TL1529; 91JHC1287), 4,5-dibenzyloxy (88USP4777252), 3-cyano (83JOC4132), and 3-cyano-4-methyl (84KGS799) derivatives of diethyl (2-pyridylamino)methylene-

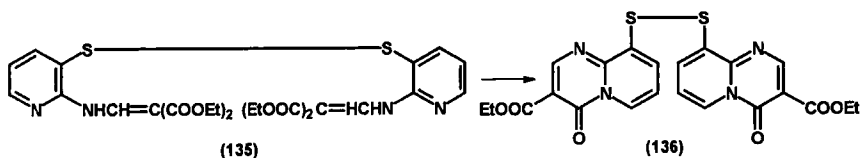


malonates **130** ( $R^1 = \text{COOEt}$ ;  $R^2 = \text{Et}$ ) by heating in diphenyl ether or in Dowtherm A at 220–250°C gave the appropriate ethyl 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **131** ( $R^1 = \text{COOEt}$ ).

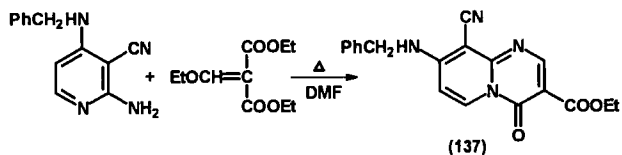
The cyclization of *N*-[3-(dimethylaminothiocarbonyloxy)-2-pyridyl]-aminomethylenemalonates **133**, prepared from dialkyl alkoxymethylenemalonates and 2-aminopyridine **132** by heating in refluxing diphenyl ether for 30 minutes, gave 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **134** (87EUP218423; 89EUP329126). In addition to ring closure, rearrangement of the substituent on the pyridine ring also occurred.



Bis(aminomethylene)malonate **135** was cyclized by heating in refluxing Dowtherm A for 5 minutes to give bis(pyrido[1,2-*a*]pyrimidin-4-one) derivative **136** (89EUP329126).



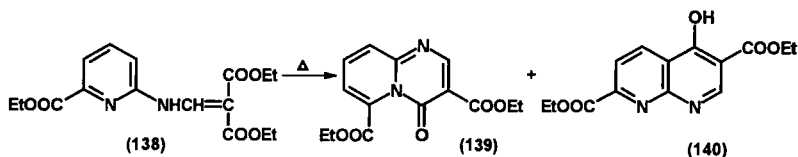
The cyclocondensation of 2-amino-4-benzylamino-3-cyanopyridine and diethyl ethoxymethylenemalonate afforded 8-benzylamino-9-cyano-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **137** in 35% yield (83KGS816).



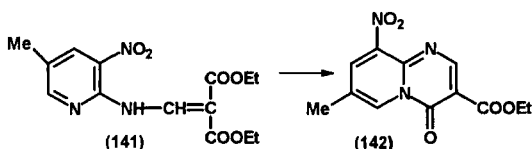
The cyclization of 3-(2-pyridylamino)acrylates **130** ( $R^2 = \text{Et}$ ) in a mixture of phosphoryl chloride–polyphosphoric acid gave the appropriate pyrido[1,2-*a*]pyrimidin-4-ones **131** when  $R^1$  was  $\text{COOEt}$ , Me, Ph, or  $\text{COCF}_3$ ; but it failed when  $R^1$  was  $\text{COMe}$  or  $\text{NO}_2$  or the substituent R was 6-NHAc and 6-OH because of tar formation (84S152).

The cyclization of the half-ester of *N*-(6-methyl-2-pyridyl)aminomethylenemalonate **130** ( $R = 6\text{-Me}$ ,  $R^1 = \text{COOH}$ ,  $R^2 = \text{Et}$ ) occurred in a shorter time than that of its diethyl ester **130** ( $R = 6\text{-Me}$ ,  $R^1 = \text{COOEt}$ ,  $R^2 = \text{Et}$ ) to give ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **131** ( $R = 6\text{-Me}$ ;  $R^1 = \text{COOEt}$ ) (84S152). The cyano and dimethyl ester derivatives of 3-aminoacrylate **130** ( $R^1 = \text{CN}$ ,  $R^2 = \text{Et}$ ;  $R^1 \text{ COOMe}$ ,  $R^2 = \text{Me}$ ) did not react under these conditions (84S152). The 6-unsubstituted derivatives of the 3-aminoacrylates **130** gave 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **131** under thermal conditions by heating in a high-boiling solvent (e.g., Dowtherm A, liquid paraffin) (e.g., 85JHC481).

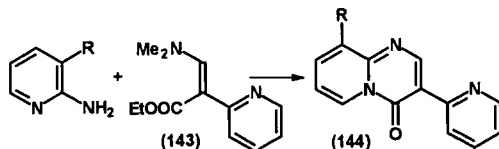
The cyclization of [(6-ethoxycarbonyl-2-pyridyl)amino]malonate **138** in Dowtherm A for 0.5 hour gave 48% 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3,6-dicarboxylate **139** and 6.8% 4-hydroxy-1,8-naphthyridine-3,7-dicarboxylate **140** (85JHC481).



Ethyl 7-methyl-9-nitro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **142** was obtained when diethyl 2-(pyridyl)aminomethylenemalonate **141** was cyclized in polyphosphoric acid at 115°C (91H1455).

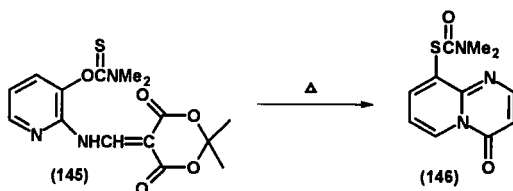


Cyclocondensation of 2-aminopyridines and ethyl 3-(dimethylamino)-2-(2-pyridyl)acrylate **143** in boiling glacial acetic acid afforded 3-(2-pyridyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **144** (93JHC1253).

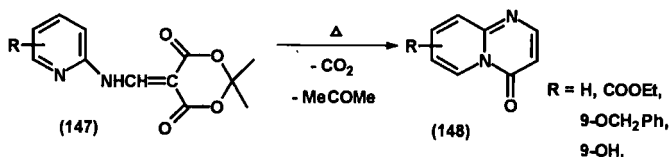


9-(Dimethylaminocarbonylthio)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **146** was obtained by the cyclization of isopropylidene *N*-[3-(dimethylamino)-

thiocarbonyloxy)-2-pyridyl]aminomethylenemalonate **145** in refluxing Dowtherm A for 5 minutes (87EUP218423).

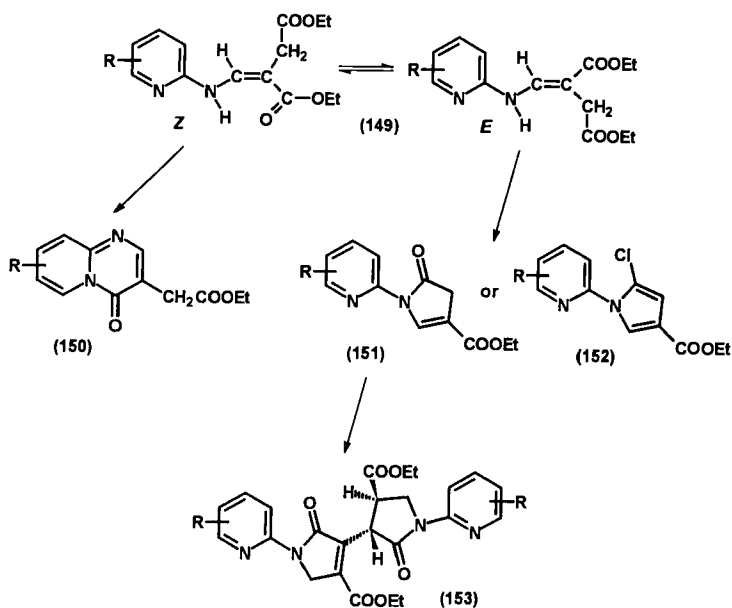


The thermal cyclization of isopropylidene 2-pyridylaminomethylenemalonates **147** by heating in diphenyl ether and Dowtherm A gave 3-unsubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **148** (84S152; 85JHC481, 85SC125; 89TL1529; 91JHC1287).



The cyclization of isopropylidene 2-pyridylaminomethylenemalonates **147** in a mixture of phosphoryl chloride–polyphosphoric acid gave 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids **131** ( $R^1 = \text{COOH}$ ) or their esters **131** ( $R^1 = \text{COOalkyl}$ ), depending upon whether the excess of phosphoryl chloride was reacted with water or an alcohol. In this way a mixed ester or a half-ester (e.g., **131**:  $R = \text{COOEt}$ ,  $R^1 = \text{COOR}^2$ ,  $R^2 = \text{H, Me}$ ) was obtained from an ester derivative of isopropylidene aminomethylenemalonate **147** ( $R = \text{COOEt}$ ) (84S152). The 6-ethoxycarbonyl derivative of isopropylidene 2-pyridylaminomethylenemalonate **147** ( $R = 6\text{-COOEt}$ ) afforded triester **138** when the reaction mixture was treated with ethanol.

The cyclization of diethyl 2-(2-pyridylaminomethylene)succinates **149** was irreversible on heating in a high-boiling solvent or in a mixture of phosphoryl chloride–polyphosphoric acid; and from both geometric isomers of compound **149** the same ratio of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetates **150** and 1-(2-pyridyl)pyrroles **151** and/or **152** was obtained [78JCS(P1)795; 80JCS(P1)227; 84JCS(P1)799, 84S152], as shown in Scheme 10. Under basic conditions at room temperature the cyclization was reversible, and the ratio of the products formed depended upon the amount of base, the reaction period, and upon the geometric isomer that was used as the starting material [84JCS(P1)1799]. In “super-dry” ethanol at ambient temperature in the presence of 3 mole equivalents of sodium ethylate, 68% of pyrido[1,2-*a*]pyrimidine **150** ( $R = \text{H}$ ) and 5% of pyridyl-



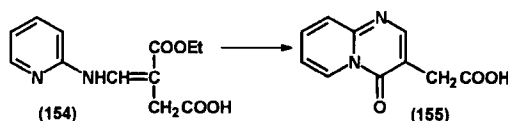
SCHEME 10

pyrrolinone **151** ( $R = H$ ) were obtained from the *Z* isomer of **149** ( $R = H$ ), while 63% of pyridylpyrrolinone **151** ( $R = H$ ) and 6% of bicyclic product **150** ( $R = H$ ) could be isolated starting from the *E* geometric isomer of **149** ( $R = H$ ) when the reaction period was 1 minute. However, 15% of pyridopyrimidine **150** ( $R = H$ ) and 54% of pyridylpyrrolinone **151** ( $R = H$ ) were formed independently of whether the *E* or *Z* isomer of **149** ( $R = H$ ) was the starting material when the reaction period was 15 minutes [84JCS(P1)1799]. The same reaction mixture could be also obtained if pyrido[1,2-*a*]pyrimidine **150** ( $R = H$ ) or pyridylpyrrolinone **151** ( $R = H$ ) was allowed to stand in ethanolic sodium ethylate for 15 minutes at ambient temperature. When a longer reaction period, 2 hours, was applied, a third product **153**, formed from pyridylpyrrolinone **151** ( $R = H$ ) by a Michael addition, could also be isolated from the reaction mixture [88JCS(P1)2019]. These results indicate that the *E*-*Z* isomerization was faster than the irreversible ring closure under thermal and acidic conditions, while under basic conditions the reversible ring-closure reactions were faster than the isomerization about the carbon-carbon double bond of 2-(2-pyridylamino)methylene)succinates **149**.

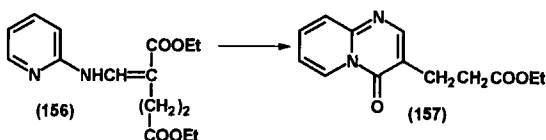
Basic conditions were favorable for the formation of all pyridylpyrrolinones **151** except the 3-substituted ones. The 3-methyl derivative

**149** ( $R = 3\text{-Me}$ ) gave only pyrido[1,2-*a*]pyrimidine **150** ( $R = 9\text{-Me}$ ), and the 3-hydroxy derivative **149** ( $R = 3\text{-OH}$ ) afforded 30% of pyrido[1,2-*a*]pyrimidine **150** ( $R = 9\text{-OH}$ ) and 10% of pyridylpyrrolinone **151** ( $R = 3\text{-OH}$ ). From the 6-substituted succinates **149** ( $R = 6\text{-Me}$ , 4,6-diMe, 6-OH, 6-NHAc) only pyridylpyrrolinones **151** ( $R = 6\text{-Me}$ , 4,6-diMe, 6-OH, 6-NHAc) were obtained. In the latter two cases the steric properties of substituents 3 and 6 might also play a role during ring closure. The 3,5-dichloro-, 3- and 5-nitro, and 5-carbamoyl derivatives of succinate **149** did not give any cyclized product under basic conditions [84JCS(P1)1799].

The mixed ethyl hydrogen 2-(2-pyridylaminomethylene)succinate **154** gave the sodium salt of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetic acid **155** in ethanolic sodium ethylate for 15 minutes at room temperature in 35% yield [88JCS(P1)2019].

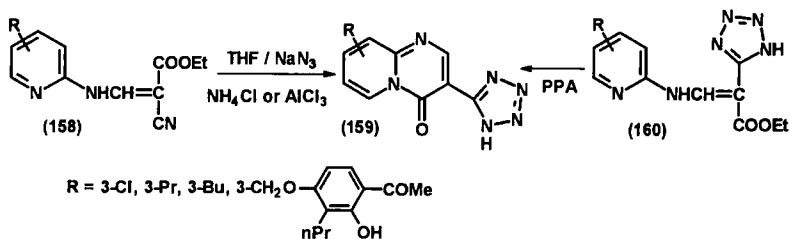


Cyclization of 2-(2-pyridylaminomethylene)glutarate **156** in ethanolic sodium ethylate for 15 minutes at room temperature afforded only 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-propionate **157** [84JCS(P1)1799]. The 6-methyl, 6-hydroxy, and 6-acetamido derivatives of glutarate **157** could not be cyclized under basic conditions.



The cyclization of ethyl [(2-pyridylamino)methylene]cyanoacetates **158** failed to give 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitriles in a mixture of phosphoryl chloride–polyphosphoric acid (84S152). They gave only poor yields of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitriles **131** ( $R^1 = \text{CN}$ ) by heating in paraffin oil at 300°C for 5 minutes (85JHC481), but proceeded smoothly by heating in tetrahydrofuran in the presence of sodium azide and aluminum chloride for 5 hours to give 3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **159** [84USP4457932; 88JAP(K)88/246374].

3-Tetrazolyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **159** ( $R = \text{H}$ ) was also claimed to be obtained by the cyclization of 3-(2-pyridylamino)-2-(5-tetrazolyl)acrylate **160** ( $R = \text{H}$ ) by heating in polyphosphoric acid at 130°C for 0.5 hours (84USP4474953), but later it was pointed out that a 1 : 1 mixture



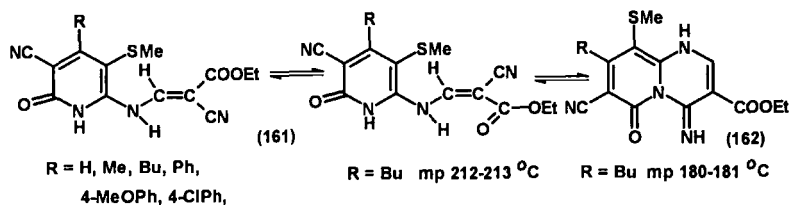
of 3-tetrazolyl-4H-pyrido[1,2-*a*]pyrimidin-4-one **159** (R = H) and its 3-(2-ethyl-2H-tetrazolyl) derivative was formed (93MIP6). Cyclization of compounds **160** was also achieved in isopropanol containing potassium hydroxide at ambient temperature for 2 hours [91JAP(K)91/74385].

The cyclization of the 3-(phenylthiomethyl)derivative of **160** (R = 3-CH<sub>2</sub>SPh) was carried out by heating in polyphosphoric acid at 110°C for 1 hour to afford 3-(tetrazol-5-yl)-4H-pyrido[1,2-*a*]pyrimidin-4-one **159** (R = 9-CH<sub>2</sub>SPh) in 8% yield (89EUP329126).

3-(Tetrazolyl)-4H-pyrido[1,2-*a*]pyrimidin-4-one **159** (R = H) was prepared in 65% yield in a one-pot reaction when 2-aminopyridine, ethyl 1H-tetrazol-5-ylacetate, triethyl orthoformate, and aluminum chloride were heated in 1,1,2,2-tetrachloroethane under nitrogen at 120°C for 3 days (84USP4474953).

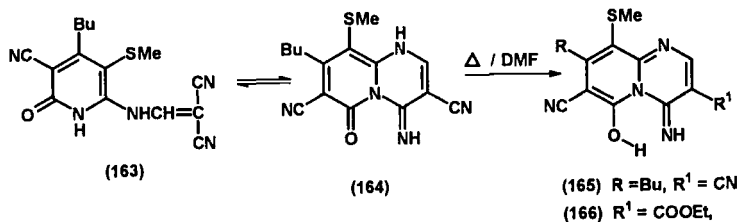
Later, it was also claimed that 3-(tetrazolyl)-4H-pyrido[1,2-*a*]pyrimidin-4-ones **159** were obtained in an one-step procedure by heating the appropriate 2-aminopyridine, ethyl (1H-tetrazol-5-yl)acetate, and triethyl orthoformate in dimethylformamide at 90°C for 1 hour, or in boiling tetrahydrofuran for 6 hours followed by treatment with 1 *N* potassium hydroxide at 50°C for 1 hour, or with anhydrous aluminum chloride under reflux for 6 hours (91EUP462834). 9-Methyl-3-(1H-tetrazolyl)-4H-pyrido[1,2-*a*]pyrimidin-4-one **159** (R = 9-Me) could be prepared when 2-amino-3-methylpyridine hydrochloride and sodium azide were suspended and stirred in dimethylformamide for 1 hour at room temperature, followed by the addition of ethyl ethoxymethylenecyanoacetate, ethoxymethylenemalononitrile, ethyl cyanoacetate and triethyl orthoformate, or malononitrile and triethyl orthoformate and stirring at 90°C for 6–12 hours. Then the reaction mixture was treated with 1 *N* potassium hydroxide at 50°C for 1 hour, phosphoryl chloride at 90°C for 5 hours, or with concentrated hydrochloric acid at 110°C for 4 hours to give 26–62% yields.

The ethyl (2-pyridylaminomethylene)cyanoacetates **161**, prepared from the appropriate 2-aminopyridine and ethyl ethoxymethylenecyanoacetate in refluxing dioxane in the presence of triethylamine, exhibited a triple tautomerism among the *E* and *Z* isomers of **161** (*E* and *Z*) and the closed-



ring form **162** in pyridine- $d_6$  (86T3537). The *Z* isomer of **161** ( $R = \text{Bu}$ ) and pyrido[1,2-*a*]pyrimidine **162** ( $R = \text{Bu}$ ) could be separated.

(2-Pyridyl)aminomethylenemalononitrile **163** also exhibited ring-chain tautomerism (86T3537).



Heating (2-pyridyl)aminomethylenecyanoacetates **161** and (2-pyridyl)aminomethylenemalononitrile **163** gave 6-hydroxy-4-imino-4*H*-pyrido[1,2-*a*]pyrimidines **165** and **166**, respectively (86T3537).

The solvent, temperature, and substituent ( $R$  and  $R'$ )-dependent ring-chain tautomerism of 2-pyridylaminomethylenemalononitriles (**167**  $\rightleftharpoons$  **168**) was studied (86JOC2988). 2-Pyridylaminomethylenemalononitriles were prepared in the reaction of 2-aminopyridines and 2-(1-ethoxyalkylidene)malononitrile in ethanol at room temperature or in a melt at  $120^{\circ}\text{C}$ , and in a one-pot reaction, starting from 2-aminopyridines, a triethyl orthoester, and malononitrile at  $110^{\circ}\text{C}$  for 10 minutes. The content of the equilibrium mixture of 2-pyridylaminomethylenemalononitrile **167** ( $R = R' = \text{H}$ ) is shown in Table X. Elevation of the temperature increased the proportion of the chain tautomer. The ratio between the two tautomeric forms **167** and **168** is influenced primarily by the steric properties of substituents  $R$  and  $R'$  in positions 6(6) and 3(9), respectively,

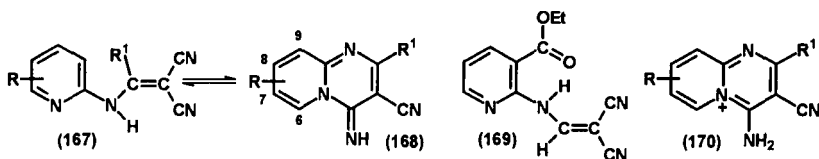


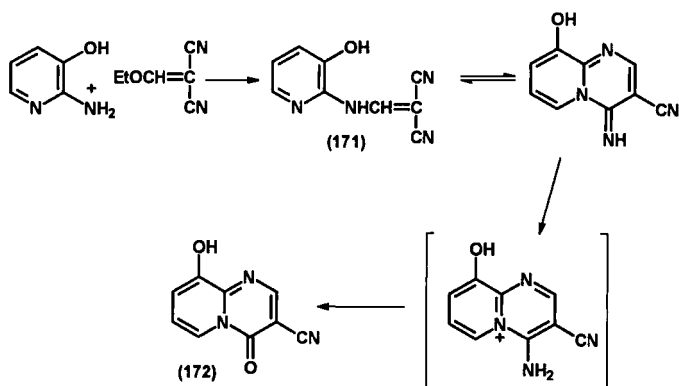
TABLE X  
EQUILIBRIUM RING-CHAIN TAUTOMERIC RATIOS FOR 4-IMINO-4*H*-  
PYRIDO[1,2-*a*]PYRIMIDINE-3-CARBONITRILE **167**  $\rightleftharpoons$  **168** ( $R = R^1 = H$ ) IN DIFFERENT  
SOLVENTS (86JOC2988)

Solvent	Temperature (°C)	Ring <b>168</b> (%)	Chain <b>167</b> (%)
CDCl <sub>2</sub> CDCl <sub>2</sub>	30	96	4
	60	92	8
	97	86	14
	124	78	22
D <sub>2</sub> O	30	95	5
CDCl <sub>3</sub>	30	80	20
CD <sub>3</sub> NO <sub>2</sub>	30	80	20
CD <sub>3</sub> CN	30	62	38
CD <sub>3</sub> OD	30	40	60
CD <sub>3</sub> COCD <sub>3</sub>	30	28	72
Me <sub>2</sub> SO- <i>d</i> <sub>6</sub>	30	5	95

and by the electronic properties of substituent *R* in positions 5(7) and 4(8). The presence of a substituent in position 6 shifted the ratio toward the chain tautomer **167** (6-*R*  $\neq$  H,  $R^1 = H$ ) to a large extent, while substituents in the side chain ( $R^1 \neq H$ ) and in position 3 favored the chain tautomer **168** [3(9)-*R*  $\neq$  H,  $R^1 \neq H$ ]. However, the presence of an ethoxycarbonyl group at position 3 of the pyridine moiety of 2-pyridylaminomethylene-malonate stabilized the chain form **169** by an internal hydrogen bond between the ester carbonyl and the NH group. An electron-donating substituent (e.g., methyl group) increased the ratio of chain tautomer, while an electron-accepting group (e.g., COOEt) increased the proportion of the chain tautomer, provided they were present at position 4(8) or 5(7). On protonation, the ring-chain equilibrium **167**  $\rightleftharpoons$  **168** was shifted toward the ring form because of the formation of a pyrido[1,2-*a*]pyrimidinium cation **170**. The acidic hydrolysis of the 4-amino group of pyrido[1,2-*a*]pyrimidinium salts **170** gave a possibility for facile preparation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives. So, when 2-amino-3-hydroxypyridine reacted with ethoxymethylenemalononitrile in dimethylformamide at 110°C for 3 hours, and the resulting *N*-(3-hydroxy-2-pyridyl)aminomethylenemalononitrile **171** was allowed to stand in a 1 : 5 mixture of concentrated hydrochloric acid and ethanol at ambient temperature for 60 hours, the hydrogen chloride salt of 3-cyano-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **172** was obtained (89EUP329126).

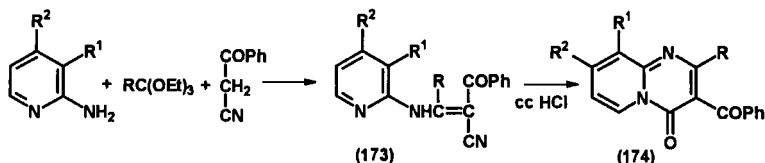
4-Imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitrile and its 7-, 8-, or 9-substituted derivatives **168** ( $R^1 = H$ ) were obtained when the appropriate 2-





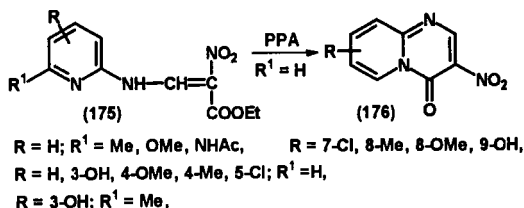
aminopyridine reacted with ethoxymethylenemalononitrile in ethanol at ambient temperature for 2 hours (90EUP385634).

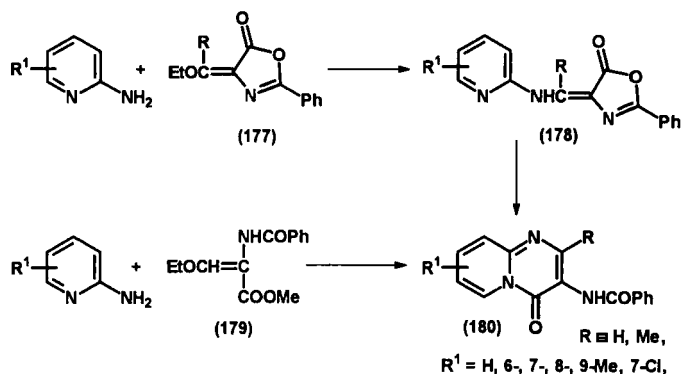
Heating 3-(2-pyridylamino)-2-benzoylacrylonitriles **173** in refluxing concentrated hydrochloric acid for 1 hour gave 3-benzoyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **174** (82S791).



3-Nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **176** were prepared by the cyclization of 6-unsubstituted 3-(2-pyridylamino)-2-nitroacrylates **175** ( $R^1 = H$ ) in polyphosphoric acid at 120°C for 1.5 hours in 50–63% yields [90JCR(S)308]. Instead of cyclizing, the 6-substituted derivatives **175** ( $R^1 \neq H$ ) decomposed under these conditions.

Clarke *et al.* reported that 2-phenyl-4-[(2-pyridylamino)methylene]-5-oxazolinone **178** ( $R = R^1 = H$ ) isomerized to 3-benzoylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **180** ( $R = R^1 = H$ ) when it stood in ethanolic sodium ethoxide in room temperature (49MI1). Later it was pointed out



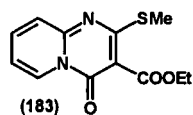
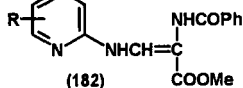
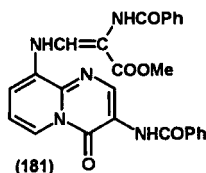


that the product was a mixture of **178** ( $\text{R} = \text{R}^1 = \text{H}$ ) and **180** ( $\text{R} = \text{R}^1 = \text{H}$ ) (84S152). The pyrido[1,2-*a*]pyrimidin-4-one **180** ( $\text{R} = \text{R}^1 = \text{H}$ ) was obtained in 90% yield when the above reaction mixture was refluxed for 1 hour (84S152). When 2-phenyl-4-[(2-pyridylamino)methylene]-5-oxazolinones **178** ( $\text{R}^1 = \text{H, 6-Me; R} = \text{H}$ ) were heated in boiling ethanol for 30 and 120 hours, pyrido[1,2-*a*]pyrimidin-4-ones **180** ( $\text{R}^1 = \text{H, 6-Me; R} = \text{H}$ ) were obtained in 88 and 38% yield, respectively (81H2149). Heating the oxazoline **178** ( $\text{R} = \text{R}^1 = \text{H}$ ) in polyphosphoric acid at 160°C for 30 minutes provided the pyridopyrimidinone **180** ( $\text{R} = \text{R}^1 = \text{H}$ ) in 30% yield (81H2149).

3-Benzamido-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **180** ( $\text{R} = \text{H}$ ) were also prepared from compound **178** ( $\text{R} = \text{H}$ ) by heating in diphenyl ether in quantitative yield [ $\text{R}^1 = 4(8)\text{-Me}$ ] (81GEP2932703) and by heating in a mixture of phosphoryl chloride–polyphosphoric acid in 64–71% yields [ $\text{R}^1 = \text{H, 6(6)-Me}$ ] (84S152).

Heating 2-amino-5-chloropyridine and 4-ethoxymethylene-5-oxazolinone **177** ( $\text{R} = \text{H}$ ) in boiling acetic acid for 4 hours or in boiling pyridine containing triethylamine for 20 hours afforded 7-chloropyrido[1,2-*a*]pyrimidin-4-one **180** ( $\text{R}^1 = 7\text{-Cl}$ ) (93H955).

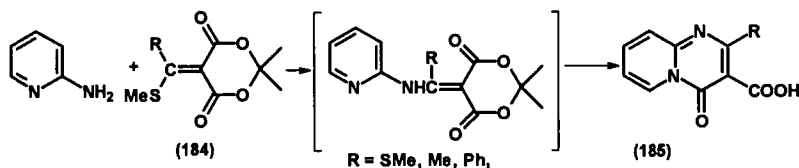
Tişler and co-workers prepared 3-benzamido-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **180** ( $\text{R} = \text{H}$ ) in the reaction of 2-aminopyridines ( $\text{R}^1 = \text{H, 3-NH}_2, 4\text{-Me}$ ) and 3-ethoxy-2-benzamidoacrylate **179** in refluxing acetic acid (90JHC359). From 2,3-diaminopyridine a condensed pyr-



ido[1,2-*a*]pyrimidin-4-one **181** was obtained. In refluxing acetic acid only 3-(2-pyridylamino)-2-benzamidoacrylate **182** could be obtained from 5-nitro-, 3,5-dibromo-, 6-methyl-, and 4,6-dimethyl derivatives of 2-aminopyridine. When the 5-nitro derivative of compound **182** ( $R = 5\text{-NO}_2$ ) reacted in pyridine with phosphoryl chloride at 70°C only 2-phenyl-4-(5-nitro-2-pyridylamino)methylene-5-oxazolinone **178** ( $R = \text{H}$ ,  $R^1 = 5\text{-NO}_2$ ) was obtained instead of the expected 3-benzoylamido-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **180** ( $R = \text{H}$ ,  $R^1 = 7\text{-NO}_2$ ).

The cyclocondensation of 2-aminopyridine and diethyl bis(methylthio)malonate at 150°C for 24 hours, then at 180°C for another 6 hours afforded ethyl 2-methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **183** in 20% yield (88CP1232904).

2-Aminopyridine and isopropylidene (methylthio)methylenemalonates **184** were reacted in refluxing ethanol to give 2-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids **185** (89S317). 2-Methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitrile was formed in the reaction of 2-aminopyridine and ethyl bis(methylthio)methylenecyanoacetate (91MI17).



#### 4. In the Reaction of Ketenes with *N*-(2-Pyridyl)formimides and Schiff Bases

Katagiri *et al.* investigated the reactions of ketenes with ethyl *N*-(2-pyridyl)formimide and Schiff bases derived from 2-aminopyridines (83CPB2899, 83H597; 84JHC407, 84MI3; 85CPB2671).

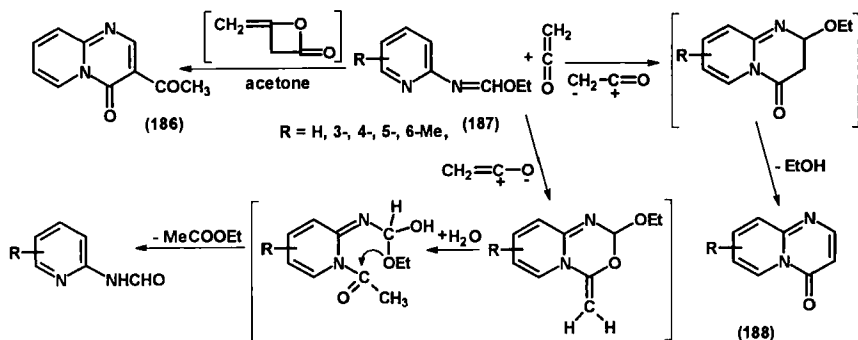
3-Acetyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **186** was formed in the reaction of ethyl *N*-(2-pyridyl)formimide **187** ( $R = \text{H}$ ) and ketene in acetone at ambient temperature for 2 days in 12% yield (83H597). It was assumed that diketene formed first from ketene, then it reacted with the formimide **187** ( $R = \text{H}$ ). When excess ketene gas was passed over formimides **187** ( $R = \text{H}$  and Me) at 75°C for 0.5–1.5 hours without solvent, 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **188** and *N*-(2-pyridyl)formamides were obtained in 25–85% and 0–45% yields, respectively. From the 5-methyl derivative of the formimide **187** ( $R = 5\text{-Me}$ ) only pyridopyrimidinone **188** ( $R = 7\text{-Me}$ ) was obtained. It was proposed that both products were formed by 1,4-

cycloaddition of ketene. When the C=C bond was involved in the reaction, pyrido[1,2-*a*]pyrimidinone **188** was formed; and when the C=O bond was used, *N*-(2-pyridyl)formamide was the product (Scheme 11).

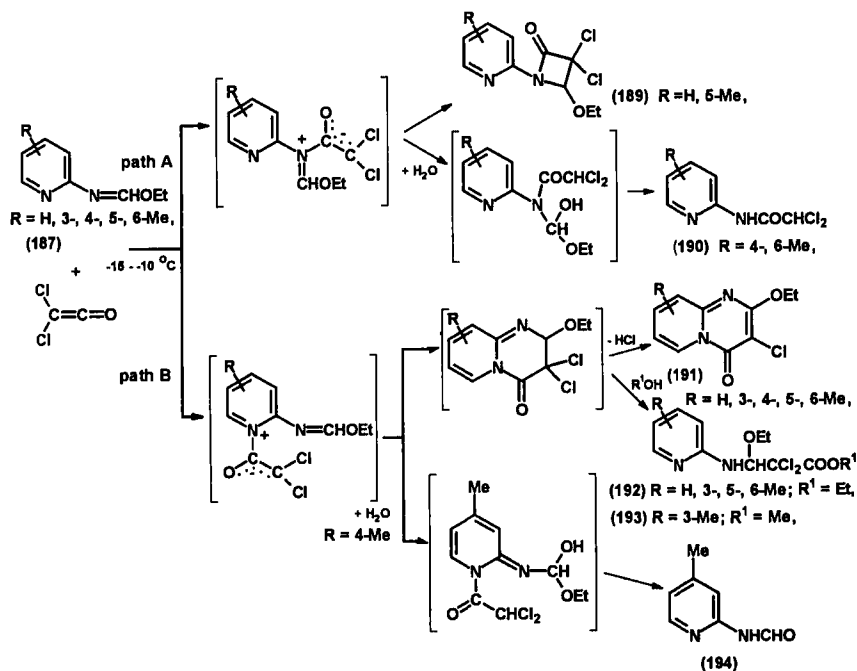
From the reaction mixture of dichloroketene, obtained from dichloroacetyl chloride with triethylamine *in situ*, and *N*-(2-pyridyl)formimides **187** in diethyl ether or in 1,2-dimethoxyethane, the following were isolated by column chromatography: 3-chloro-2-ethoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **191** in 21–47% yields, ethyl 2,2-dichloro-3-ethoxy-3-(2-pyridylamino) propionates **192** in 11–51% yields, 3,3-dichloro-4-ethoxy-1-(2-pyridyl)-2-azetidinones **189** in 7% yield, 2-(2,2-dichloroacetamido)-pyridines **190** in 2–9% yields, and/or *N*-(4-methyl-2-pyridyl)formamide **194** in 9% yield (83CPB2899). When the 3-methyl derivative of formimide **187** (*R* = 3-Me) reacted with dichloroketene in the presence of excess triethylamine, only 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **191** (*R* = 9-Me) was obtained. When methanol was added to the reaction mixture, 9-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **191** (*R* = 9-Me) and the methyl ester of 3-ethoxy-2,2-dichloro-3-(3-methyl-2-pyridyl)propionate **192** (*R* = 3-Me, *R*<sup>1</sup> = Me) was prepared in 25% and 65% yields, respectively. The formation of products **189–194** was suggested to start by the attack of the carbonyl group of the dichloroketene on the amino and ring nitrogens to follow path A and path B, respectively, in Scheme 12.

In a similar way *N*-(2-pyridyl)formimides **187** (*R* = H, 3-Me) in methylene chloride were reacted with chloroketene **195**, prepared from the appropriate carboxylic acid with trifluoroacetic anhydride followed by treatment of the mixed anhydride with triethylamine *in situ*, to give 3-ribofuranosyl-2-ethoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **196** (*R* = H, 3-Me) and enamine **197** in 10–17% yields, respectively (84MI3; 85CPB2671).

The cyclocondensation of Schiff bases **198** in diethyl ether and dichloro-

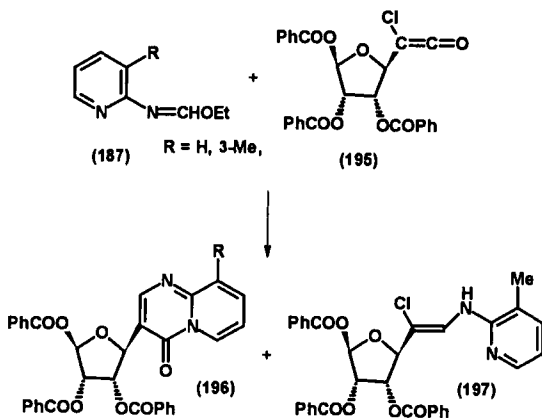


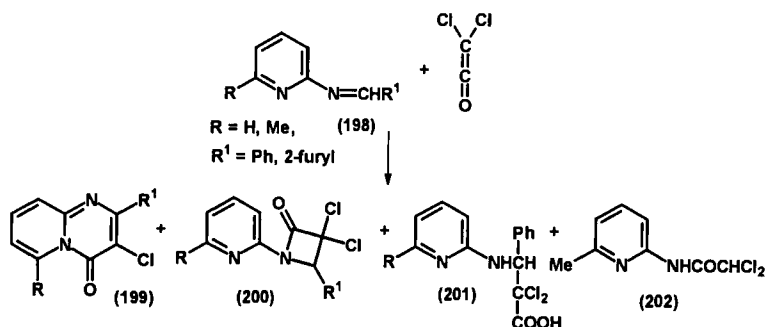
SCHEME 11



SCHEME 12

ketene, prepared *in situ* from dichloroacetyl chloride with triethylamine, gave 2-substituted 3-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **199**, 4-substituted 3,3-dichloro-1-(2-pyridyl)-2-azetidinones **200**, and 3-(2-pyridyl)-3-phenyl-2,2-dichloropropionic acids **201** in 39–78%, 3–9%, and 6–13%





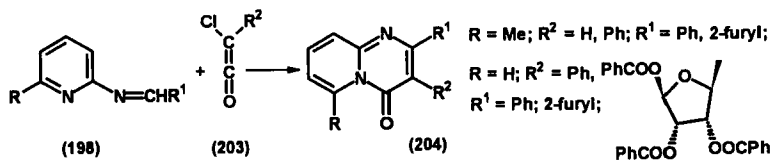
yields, respectively (84JHC407). From the reaction mixture of the 6-methyl derivative **198**, ( $\text{R} = \text{Me}$ ,  $\text{R}^1 = 2\text{-furyl}$ ), 2-(2,2-dichloroacetamido)-6-methylpyridine **202** was also isolated in 17% yield.

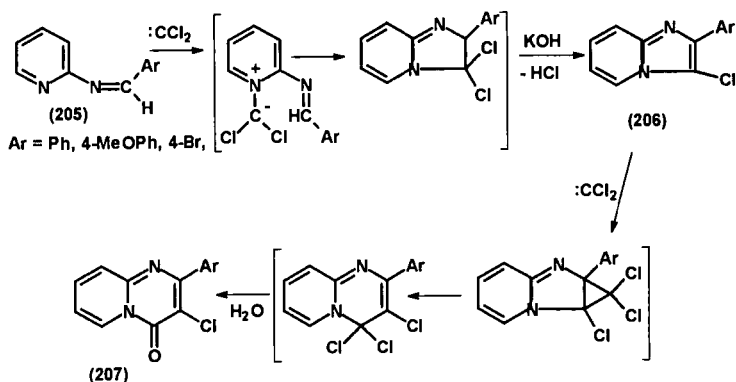
When methanol was added to the ethereal reaction mixtures of benzyldene derivatives of 2-aminopyridines **198** ( $\text{R} = \text{H, Me}$ ;  $\text{R}^1 = \text{Ph}$ ) and the reaction mixtures were allowed to warm up to ambient temperature and left to stand overnight, 3-chloro-2-phenyl-4H-pyrido[1,2-*a*]pyrimidin-4-ones **199** ( $\text{R} = \text{H, Me}$ ;  $\text{R}^1 = \text{Ph}$ ) and the methyl esters of propionic acids **201** were obtained in 5–10% and 18–32% yields, respectively (84JHC407).

From the reaction of benzyldene derivative **198** ( $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{Ph}$ ) and dichloroketene in 1,2-dimethoxyethane, 3-chloro-2-phenyl-4H-pyrido[1,2-*a*]pyrimidin-4-one **199** ( $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{Ph}$ ), azetidine **200** ( $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{Ph}$ ), and propionic acid **201** ( $\text{R} = \text{H}$ ) were isolated in 45%, 10%, and 2% yields, respectively (84JHC407).

The cyclocondensation of Schiff bases **198** and chloroketenes **203** prepared from the appropriate acid chloride with triethylamine *in situ* in diethyl ether or in 1,2-dimethoxyethane afforded 4H-pyrido[1,2-*a*]pyrimidin-4-ones **204** in 20–40% yields (84JHC407, 84MI3; 85CPB2671).

Reaction of Schiff bases **205** and dichlorocarbene, generated *in situ* from chloroform with potassium hydroxide, in the presence of benzyltriethylammonium chloride at 20°C for 5–12 hours under argon afforded imidazo[1,2-*a*]pyrimidines **206** and 4H-pyrido[1,2-*a*]pyrimidin-4-ones **207** in 34–40% and 1–20% yields, respectively (91KGS810). 4H-Pyrido[1,2-



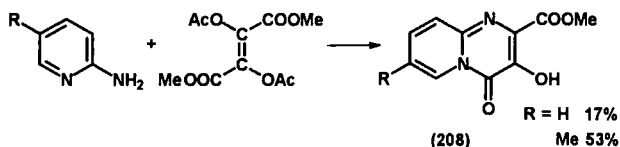


SCHEME 13

*a*]pyrimidin-4-ones **207** were probably formed from imidazo[1,2-*a*]pyridines **206** with a second mole of dichlorocarbene (Scheme 13).

### 5. Miscellaneous Syntheses

The cyclocondensation of 2-aminopyridines and dimethyl diacetoxyfumarate in refluxing methanol in the presence of *p*-toluenesulfonic acid for 3 hours gave 3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **208** (90OPP532).

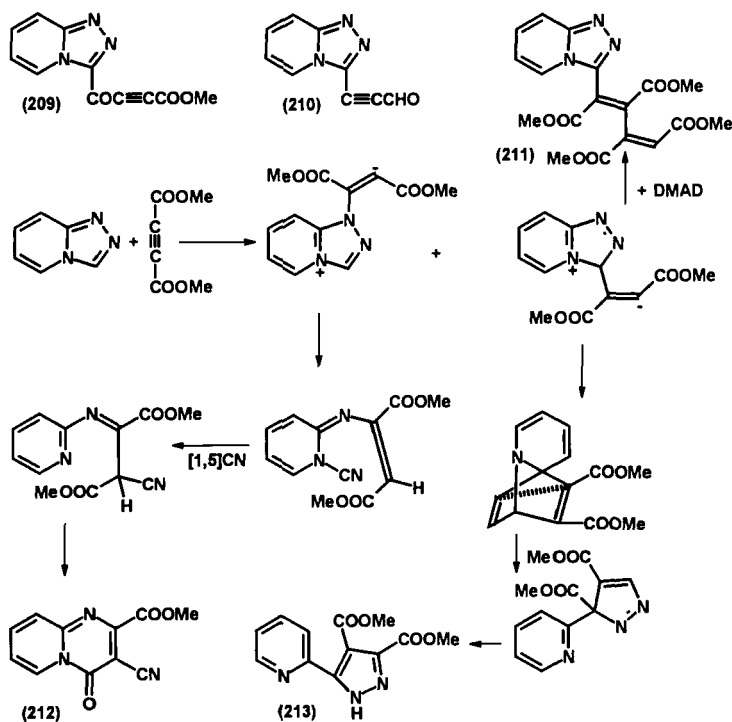


Heath and Rees corrected the earlier conclusions of Potts *et al.* (66JOC265) and Sai *et al.* [81IJC(B)10] who had reacted 1,2,4-triazolo[4,3-*a*]pyridine with dimethyl acetylenedicarboxylate in boiling toluene and benzene. The latter believed that 3-substituted triazolopyridines **209** and **210** were the products. Heath and Rees repeated the experiments in refluxing benzene and in refluxing toluene both in the presence and absence of 5% palladium-on-charcoal, and showed that under all sets of conditions 3-cyano-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate **212**, 5-(2-pyridyl)pyrazole-3,4-dicarboxylate **213**, and an adduct **211** were isolated from the complex reaction mixtures in 20%, 20%, and 1% yields, respectively (82CC1280). When the reaction was carried out in methanol, only 3-cyano-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate **212** was obtained

in 70% yield. The proposed reaction mechanism is depicted in Scheme 14. Compound **209** proved to be pyrido[1,2-*a*]pyrimidinone **212**, while compound **210** was probably 3-cyano-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, which might be formed from 2-ester derivative **212** by hydrolysis and decarboxylation during work-up.

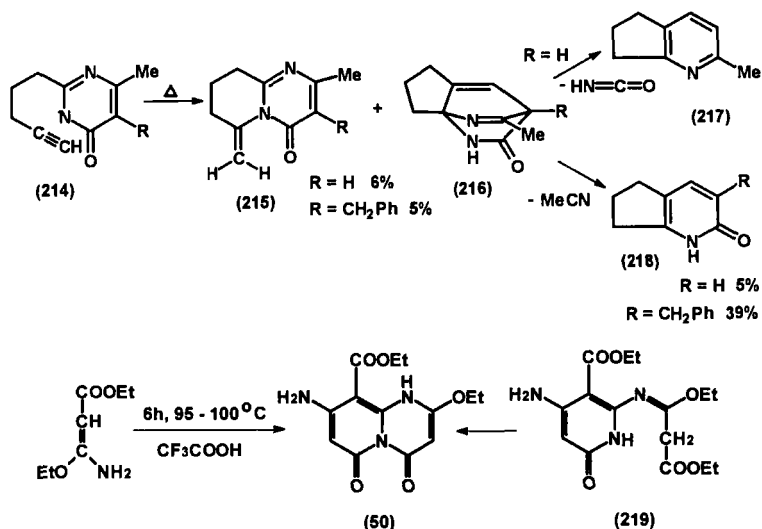
Heating acetylenic pyrimidinones **214** in refluxing naphthalene for 1–2 hours gave 6-methylene-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **215** and tricyclic intermediates **216** (83JHC1407). The latter **216** decomposed under the reaction conditions to give cyclopentano(*b*)pyridine **217** and cyclopentano(*b*)pyridinones **218** by elimination of  $\text{HN}=\text{C}=\text{O}$  and acetonitrile, respectively.

Pyrido[1,2-*a*]pyrimidine-4,6-dione **50** could be isolated in 2% yield from the reaction mixture of the acid-catalyzed self-condensation of ethyl 3-amino-3-ethoxyacrylate along with other monocyclic products (83LA753). Better yield (54%) was achieved when pyridine derivative **219** was heated in dimethylformamide in the presence of *p*-toluenesulfonic acid at 110°C.

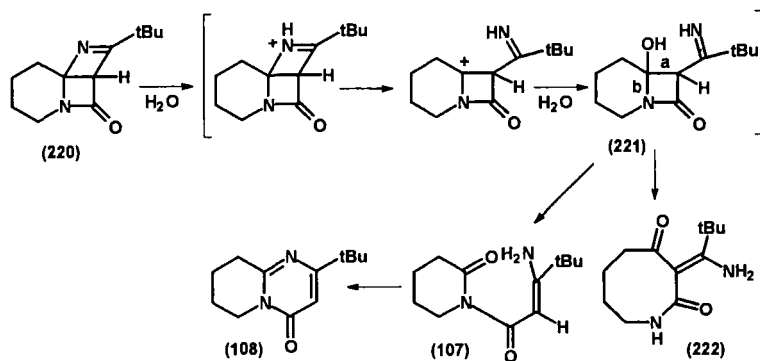


SCHEME 14

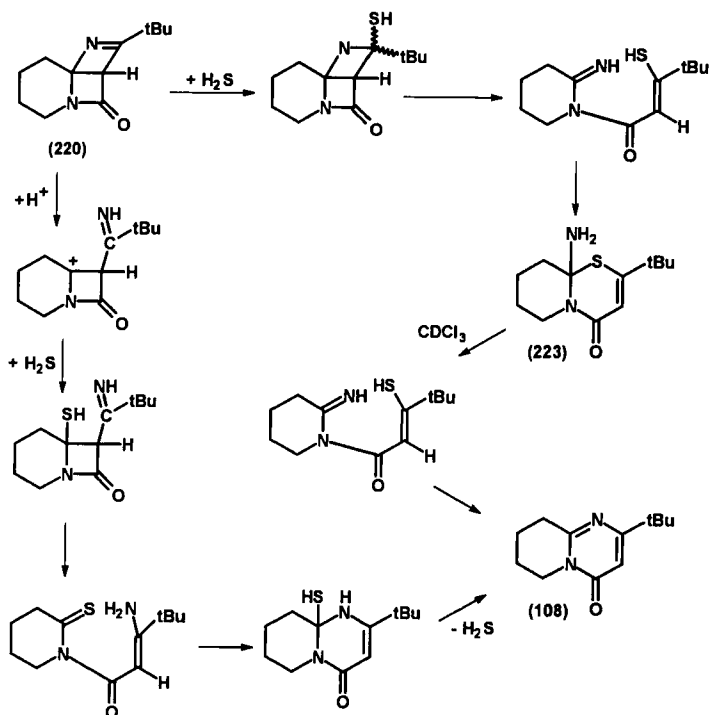




The reaction of Dewar pyrimidinone **220** with water in 1:9 mixture of water and acetone at 20°C for 1 hour afforded 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **108** and enamine **107** in 34% and 64% yields, respectively [89JCS(P1)1231]. Enamine **107** was formed by the cleavage of bond *a* of 4-hydroxyazetidino-2-one **221**, and ring closure of enamine **107** by elimination of water gave 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **108** (Scheme 15). When the solvent polarity was increased, the cleavage of bond *b* of 4-hydroxyazetidino-2-one **221** also occurred. The reaction in aqueous acetonitrile-*d*<sub>3</sub> at 35°C for 37 hours gave 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **109** and lactam **222** in 85% and 10% yields, respectively. The reaction of Dewar



SCHEME 15



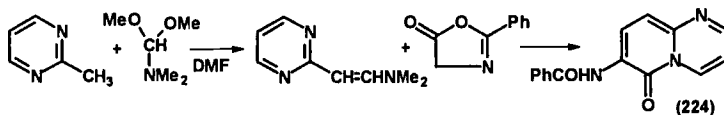
SCHEME 16

pyrimidinone **220** and  $\text{H}_2\text{S}$  in acetonitrile at  $0^\circ\text{C}$  for 15–17 hours afforded 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **108** and 4*H*-pyrido[2,1-*b*][1,3]thiazin-4-one **223** in 32% and 52% yields, respectively (Scheme 16). When 4*H*-pyrido[2,1-*b*][1,3]thiazin-4-one **223** was set aside in  $\text{CDCl}_3$  at  $35^\circ\text{C}$  for 88 hours, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **108** was obtained in 98% yield.

### E. 6-Oxo-6*H*-PYRIDO[1,2-*a*]PYRIMIDINES

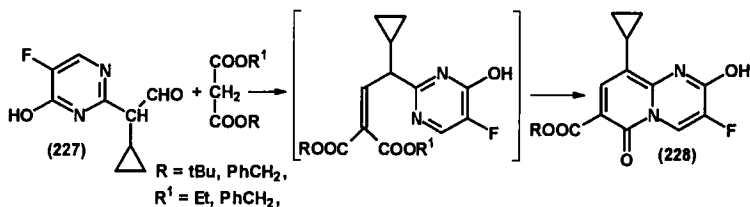
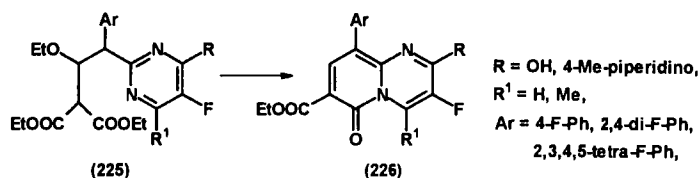
7-Benzoylamino-6*H*-pyrido[1,2-*a*]pyrimidin-6-one **224** was prepared starting from 2-methylpyrimidine and *N,N*-dimethylformamide dimethylacetate in boiling dimethylformamide (91BSB533). Then the resulting 2-[(*E*)-2-(*N,N*-dimethylamino)ethenyl]pyrimidine was reacted with 2-phenyl-5(4*H*)-oxazolone in refluxing acetic acid to give 6-oxopyrido[1,2-*a*]pyrimidine **224** in 33% yield.

6-Oxo-6*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylates **226** were prepared



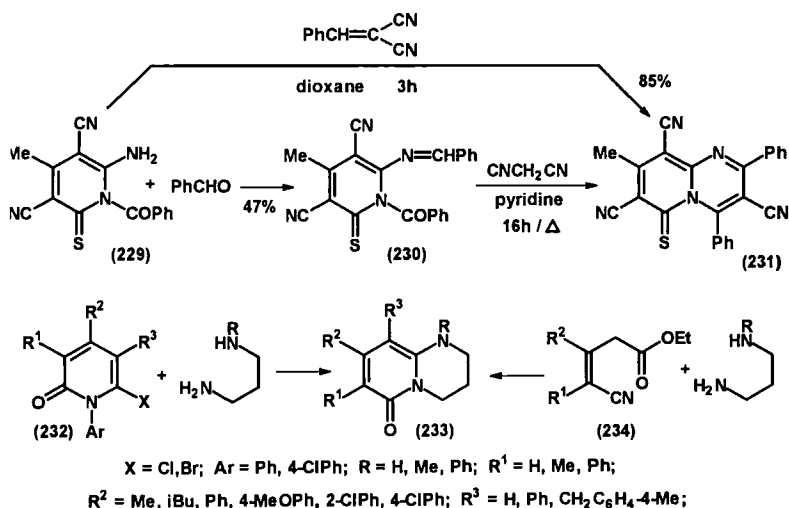
by the cyclization of pyrimidine derivatives **225** in boiling toluene in the presence of DBU for 16–20.5 hours in 19–55% yields, in boiling ethanol in the presence of a catalytic amount of piperidine and acetic acid for 3–16 hours in 30–84% yields, or in boiling ethanol in the presence of a catalytic amount of concentrated sulfuric acid for 18 hours in 53% yield (91MIP3; 93MI20). Besides cyclization, elimination of ethanol also occurred.

Cyclocondensation of malonates and acetaldehyde derivative **227** in boiling ethanol in the presence of catalytic amounts of piperidine and acetic acid under nitrogen also afforded 6-oxo-6*H*-pyrido[1,2-*a*]-pyrimidine-7-carboxylates **228** (91MIP3).



6*H*-Pyrido[1,2-*a*]pyrimidine-6-thione **231** was prepared in the reaction of pyridinethione **229** and benzylidenemalononitrile in boiling dioxane in the presence of a catalytic amount of piperidine [93JCR(S)8]. 6*H*-Pyrido[1,2-*a*]pyrimidine-6-thione **231** was also obtained when pyridinethione **229** was reacted with benzaldehyde in the presence of a few drops of piperidine for 2 hours, and then condensation product **230** was reacted with malononitrile.

1,2,3,4-Tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-ones **233** were prepared in the reaction of 1,3-diaminopropanes with 6-halo-1-aryl-1*H*-pyridone **232** in refluxing 2-ethoxyethanol for 1–50 hours or with ethyl 4-cyano-3-butenates **234** in boiling 1,2-dimethoxyethane for 12 hours or

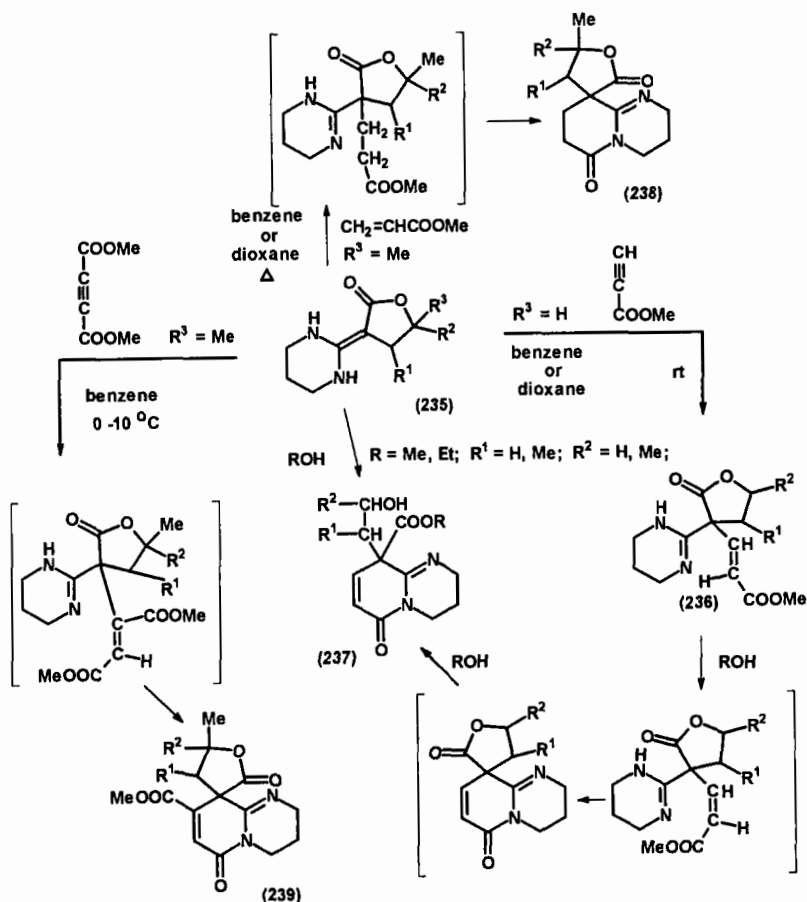


in *o*-dichlorobenzene at 120–180°C for 2–24 hours in moderate yields (81USP4284778; 82BRP1588166).

Wamhoff and Huang obtained alkyl 2,3,4,9-tetrahydro-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylates **237** in the reaction of 3-(hexahydropyrimidin-2-ylidene)-2(3*H*)-furanones **235** ( $\text{R}^3 = \text{H}$ ) and methyl propiolate in a refluxing alcohol in excellent yields (Scheme 17) (84CB1856). When the reactions were carried out in benzene or dioxane, addition products **236** could be isolated, which then were transformed in quantitative yields to tetrahydro-6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylates **237** by stirring in an alcohol at ambient or elevated temperature. When 3-(hexahydropyrimidin-2-ylidene)-2(3*H*)-furanones **235** ( $\text{R}^3 = \text{Me}$ ) were reacted with methyl acrylate or with dimethyl acetylenedicarboxylate, hexahydro- and tetrahydropyridopyrimidin-6-ones **238** and **239**, respectively, were obtained in good yields (84CB1926).

Later Huang *et al.* extended the above reaction for the preparation of 9-substituted 1,2,3,4-tetrahydro- and 1,2,3,4,7,8-hexahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-ones (**242**, **243**, **245**, **249**, and **250**) starting from ketene amins (**240**, **244**, and **247**) and alkyl propiolate, dimethyl acetylenedicarboxylate, or methyl acrylate [86H2247; 87CB1803, 87TL1527; 89SC1801; 93JCS(P1)1085, 93SC1039; 94H1233].

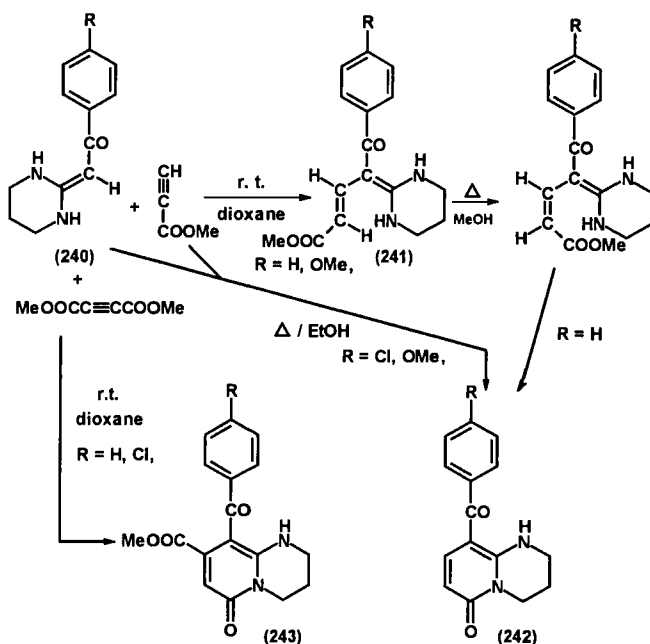
The reaction of ketene amins **240** and methyl propiolate for 2 days gave addition products **241** in near-quantitative yields (Scheme 18). During the heating of addition product **241** ( $\text{R} = \text{H}$ ) in methanol for 16 hours, first *cis-trans* isomerization then ring closure occurred to give tetrahydropyrido[1,2-*a*]pyrimidin-6-one **242** ( $\text{R} = \text{H}$ ) (86H2247). When the reac-



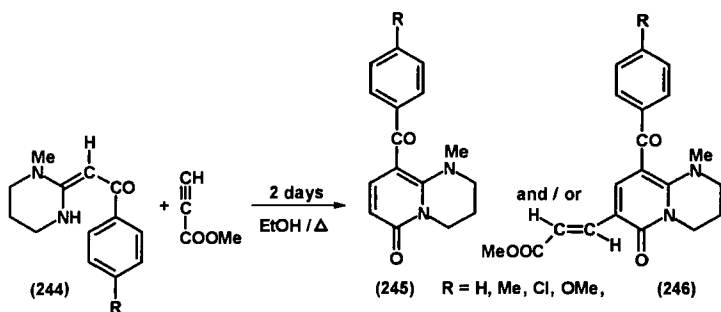
SCHEME 17

tion of ketene aminals **240** and methyl propiolate was carried out in refluxing ethanol for 36 hours, pyrido[1,2-*a*]pyrimidin-6-ones **242** were obtained in a one-pot reaction (89SC1801). The reaction of ketene aminals **240** and the more reactive dimethyl acetylenedicarboxylate in dioxane at room temperature for 2 days afforded 6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-8-carboxylates **243** (86H2247). In these cases no intermediates could be isolated.

When *N*-methyl ketene aminals **244** reacted with ethyl propiolate in 1 : 1 mole ratio, 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-ones **245** were obtained as the main products (35–58%) together with a low yield of (6-oxo-6*H*-pyrido[1,2-*a*]pyrimidin-7-yl)acrylates **246** (5–7%) [93JCS(P1)-

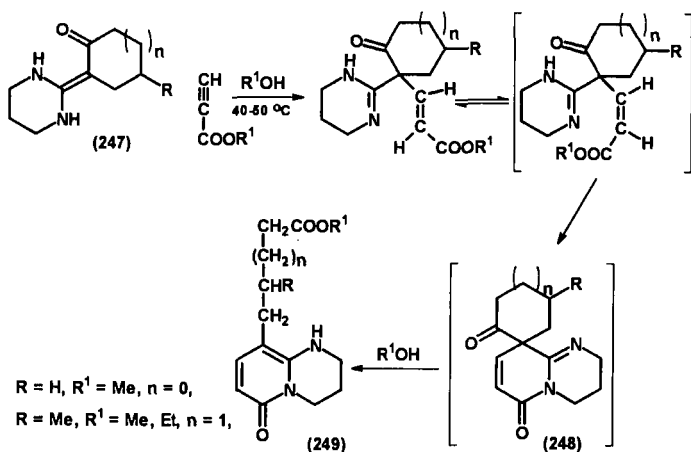


SCHEME 18



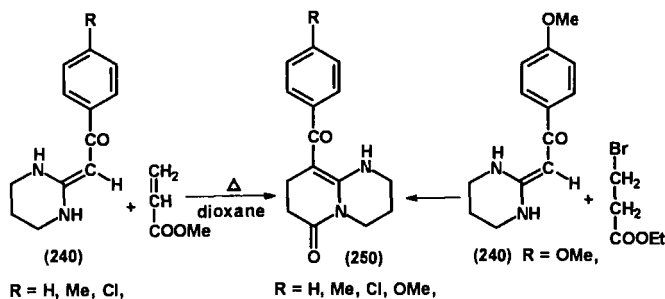
1085]. When the molar ratio was changed from 1:1 to 1:8, only (pyrido[1,2-*a*]pyrimidin-7-yl)acrylates **246** were obtained.

In the reaction of 2-(hexahydropyrimidin-2-ylidene)cycloalkanone **247** and alkyl propiolate for 20–40 hours, after addition and *cis-trans* isomerization, the spiro intermediates **248** suffered ring cleavage by the attack of a molecule of alcohol to give alkyl 6-oxo-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidine-9-alkanoates **249** (Scheme 19) (87CB1803, 87TL1527).



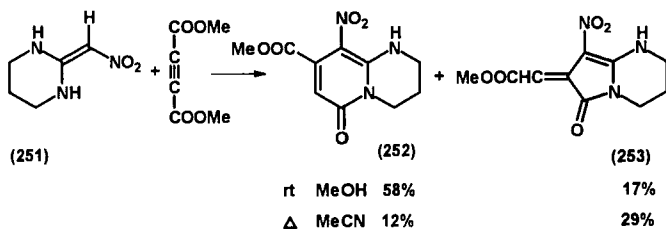
SCHEME 19

Methyl acrylate did not react with ketene aminals **240** ( $R = \text{Me}, \text{Cl}$ ) in dioxane at ambient temperature, but reactions took place on refluxing for 20–48 hours to yield hexahydro-6H-pyrido[1,2-a]pyrimidin-6-ones **250** ( $R = \text{Me}, \text{Cl}$ ) (86H2247; 89SC1801). Hexahydro-6H-pyrido[1,2-a]pyrimidin-6-one **250** ( $R = \text{OMe}$ ) was also prepared in the reaction of ketene aminal **240** ( $R = \text{OMe}$ ) and ethyl 3-bromopropionate in refluxing acetonitrile for 48 hours (89SC1801). Hexahydro-6H-pyrido[1,2-a]pyrimidin-6-ones **250** ( $R = \text{H}, \text{Me}, \text{Cl}, \text{OMe}$ ) were prepared in better yields (79–91%) when the reaction mixture of ketene aminal **240** ( $R = \text{H}, \text{Me}, \text{Cl}, \text{OMe}$ ) and an excess of methyl acrylate was irradiated in anhydrous methanol by a 450-W medium-pressure mercury lamp under nitrogen at ambient temperature for 3–5 hours (93SC1039).

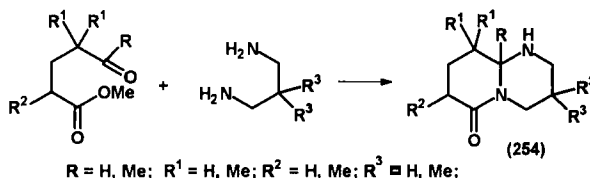


Reaction of 2-nitromethylenehexahydropyrimidine **251** with dimethyl acetylenedicarboxylate in methanol at ambient temperature for 15 hours

gave pyrido[1,2-*a*]pyrimidin-6-one **252** and pyrrolo[1,2-*a*]pyrimidinone **253** in about a 3 : 1 ratio, while in acetonitrile at reflux for 3 hours the ratio was 1 : 2 (93BCJ2118).



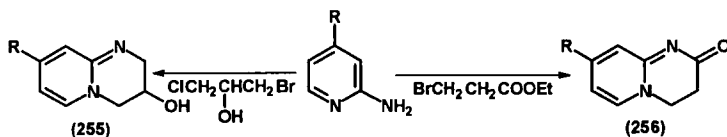
Perhydropyrido[1,2-*a*]pyrimidin-6-ones **254** were synthesized in the reaction of 1,3-diaminopropanes and methyl 4-acylbutanoates in boiling ethanol (82EUP65724).



#### F. 3,4-DIHYDRO-2*H*- AND 2-OXO-3,4-DIHYDRO-2*H*-PYRIDO-[1,2-*a*]PYRIMIDINES

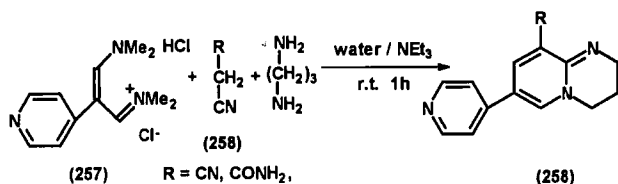
3-Hydroxy-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine hydrobromide and its 8-methyl derivative **255** ( $\text{R} = \text{H, Me}$ ) were obtained in the reaction of appropriate 2-aminopyridine and 1-bromo-3-chloro-2-propanol in refluxing dimethylformamide for 3.5 hours (84MI17).

By the reaction of 2-aminopyridines with ethyl 3-bromopropionate in dimethylformamide at 130–150°C for 3–5 hours 2-oxo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines **256** were prepared (84MI17).



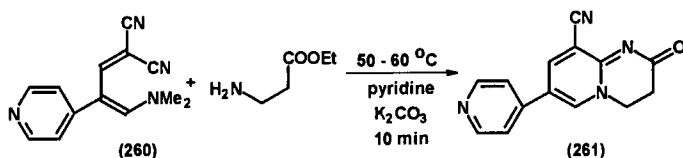
Reaction of *N,N*-dimethyl-*N*-[3-dimethylamino-2-(4-pyridyl)prop-2-enylidene]ammonium chloride hydrochloride **257** with CH acid com-



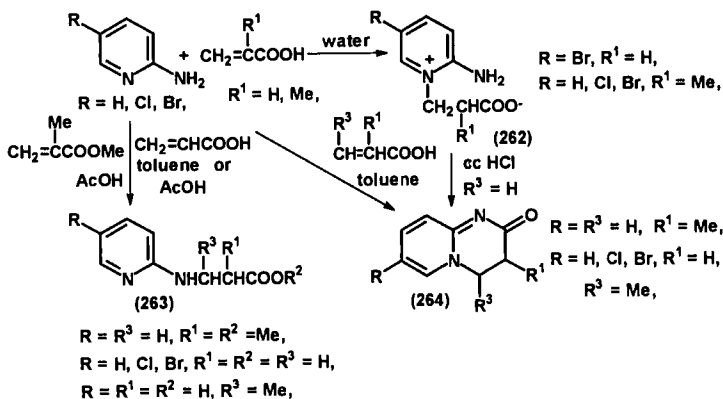


pounds **258** and 1,3-diaminopropane gave 7-(4-pyridyl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines **259** in 7–17% yields (90EGP279020).

3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one **261** was prepared in 42% yield when dinitrile **260** was reacted with  $\beta$ -alanine methyl ester hydrochloride (90EGP279020).



Reaction of 2-aminopyridines with acrylic acid or methacrylic acid in boiling water for 2–20 hours gave betaine hydrates **262** ( $\text{R}^3 = \text{H}$ ) in 11–88% yields (Scheme 20) (92KGS80). When 2-aminopyridine reacted with methyl methacrylate in acetic acid for 24 hours or 2-aminopyridine and its 5-bromo and 5-chloro derivatives reacted with acrylic acid in boiling toluene for 24 hours or 2-aminopyridine reacted with crotonic acid in boiling toluene for 20 hours, 3-(2-pyridylamino)propionic acid derivatives **263** were the products. When 5-chloro-2-aminopyridine reacted with acrylic

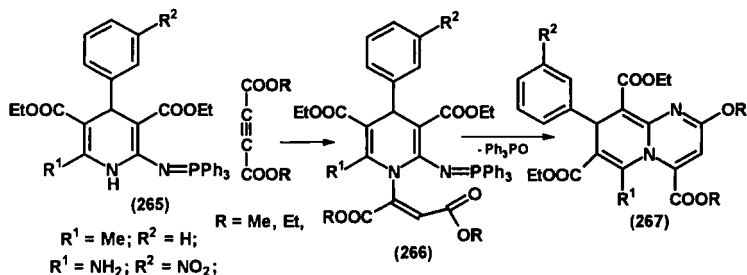


SCHEME 20

acid in boiling water for 20 hours, 3-(2-pyridylamino)propionic acid **263**, ( $R = Cl$ ,  $R^1 = R^2 = R^3 = H$ ) and betaine **262** ( $R = Cl$ ,  $R^1 = R^3 = H$ ) could be isolated from the reaction mixture in 62% and 14% yields, respectively. 3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **264** were obtained when a mixture of 2-aminopyridine and methacrylic acid or crotonic acid was heated in boiling toluene under a water separator for 20 hours. Betaines **262** ( $R = H$ ,  $Cl$ ,  $Br$ ;  $R^1 = Me$ ;  $R^3 = Me$ ) were also cyclized into hydrochlorides of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones **264** when heated in concentrated hydrochloric acid. A solution of betaine **262** ( $R = R^3 = H$ ,  $R^1 = Me$ ) heated in toluene under a water separator for 1 hour gave 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one **264** ( $R = R^3 = H$ ,  $R^1 = Me$ ).

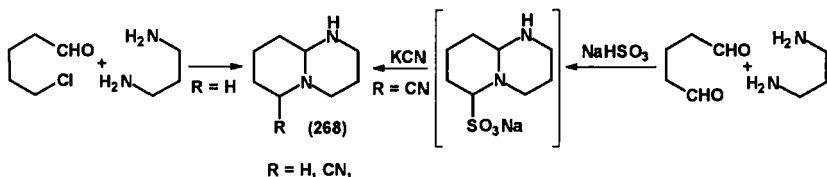
### G. MISCELLANEOUS PYRIDO[1,2-*a*]PYRIMIDINES

The Aza-Wittig reaction of the adducts **266** of 2-(triphenylphosphoranylideneamino)-1,4-dihydropyridines **265** and dialkyl acetylenedicarboxylates in dioxane or toluene gave 8*H*-pyrido[1,2-*a*]pyrimidine-4,7,9-tricarboxylates **267** (90LA901).



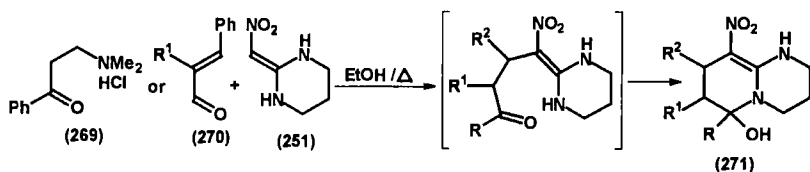
Perhydropyrido[1,2-*a*]pyrimidine (**268**,  $R = H$ ) hydrochloride was obtained in the reaction of 5-chloropentanal and 1,3-diaminopropane in methylene chloride in the presence of magnesium sulfate (82TL4181; 93JA6580).

6-Cyanoperhydropyrido[1,2-*a*]pyrimidine **268** ( $R = CN$ ) was prepared

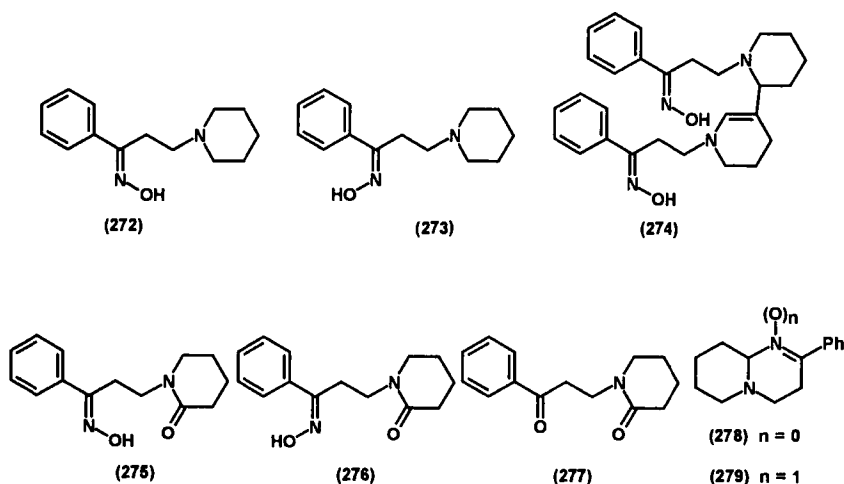


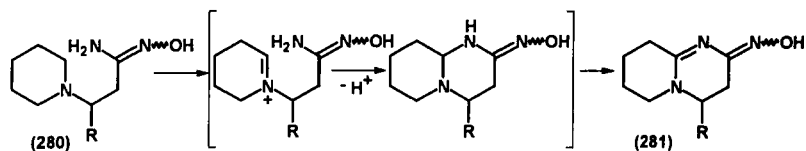
when potassium cyanide was added to an aqueous reaction mixture of glutacon aldehyde, 1,3-diaminopropane, and sodium bisulfite that had been left to stand at ambient temperature for 16 hours, after which the reaction mixture was left to stand for another 24 hours at room temperature [87JAP(K)87/209078].

Reaction of 2-(nitromethylene)hexahydropyrimidine **251** with the hydrochloride of dimethylamino ketone **269** or  $\alpha,\beta$ -unsaturated ketone **270** afforded 9-nitrohexahydro-2*H*-pyrido[1,2-*a*]pyrimidines **271** (93AP335).

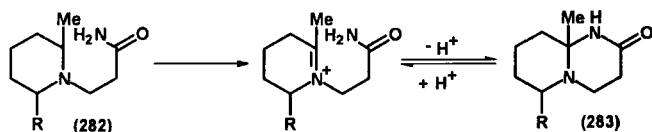


The dehydrogenation of (*E*)- and (*Z*)- $\omega$ -piperidinopropiophenone oximes **272** and **273** with mercuric acetate–EDTA was investigated by Möhrle and Schmidt (82AP1032). From the reaction mixture of *Z* isomer **272**, *Z* and *E* isomers of 1-(3-hydroximino-3-phenylpropyl)-2-piperidone **275** and **276** and dimerized product **274** were isolated in 18% trace, and 24.8% yields, respectively. With six oxidation equivalents, *E* isomer **272** gave bicyclic products **278** and **279** and propiophenone derivatives **275**, **276**, and **277** in 9.3%, 16.4%, 4.1%, 18.1%, and 8.1% yields, respectively. When the reaction was carried out with four equivalents of oxidation agent, the *N*-oxide **279** was isolated in 44% yield. Oxidation of piperidino-

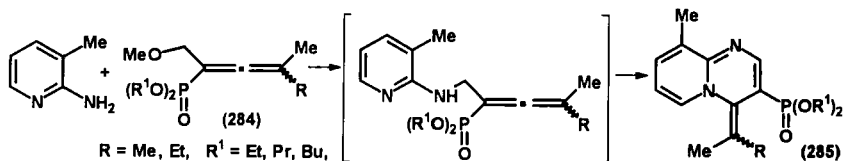




propionamidoximes **280** with mercury(II)–EDTA complex gave a mixture of *E* and *Z* isomers of 2-(hydroxyimino)pyrido[1,2-*a*]pyrimidines **281** (92AP23). Oxidation of 3-piperidinopropionamides **282** with mercury(II)–EDTA complex gave perhydropyrido[1,2-*a*]pyrimidin-2-ones **283** which exhibited ring–chain tautomerism (92AP177).



Cyclocondensation of 2-amino-3-methylpyridine and allenephosphonates **284** by stirring the reaction mixture in the absence of a solvent at 35–40°C for 48 hours afforded 4-methylene-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines **285** (90DOK619; 91IZV473). The ethyl derivatives **285** (R = Et) were obtained as *E* and *Z* geometric mixtures.

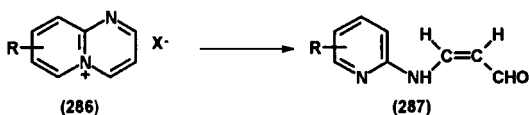


## IV. Reactions of Pyrido[1,2-*a*]pyrimidines

### A. PYRIDO[1,2-*a*]PYRIMIDINIUM SALTS

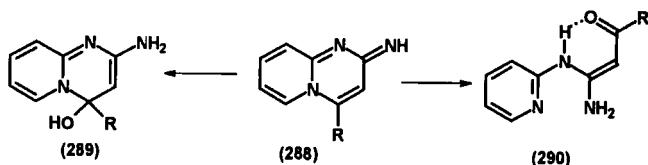
Pyrido[1,2-*a*]pyrimidinium salts **286** easily suffered hydrolytic ring opening in basic media to give 3-(2-pyridylamino)acroleins **287** (86EUP174832).

The secondary amino group of 3-(*N*-ethylaminomethyl)-7-[2-(2-aminothiazol-4-yl)-2-(*Z*-1-carboxy-1-methylethoxyimino)acetamido]ceph-3-em-3-carboxylic acid was arylated with 8-methylthiopyrido[1,2-*a*]pyrimidinium salt in dimethylformamide in the presence of triethylamine at 40°C (89MIP2).



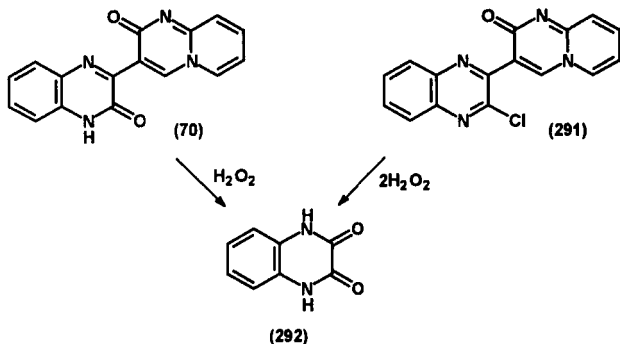
### B. 2-Oxo-2*H*-PYRIDO[1,2-*a*]PYRIMIDINES

The treatment of 2-imino-4-alkyl-2*H*-pyrido[1,2-*a*]pyrimidine hydrochlorides **288** with sodium carbonate in 95% ethanol at room temperature for 10 hours gave 4-hydroxyl-4-alkyl derivatives **289** as hydrates [88JCS(P1)975]. If the reaction mixtures were refluxed for 24 hours, then ring-opened products **290** were isolated. The presence of a hydroxyl group at position 9 increased the stability of bicyclic **289**.



The oxidation of quinoxaline derivatives of 2*H*-pyrido[1,2-*a*]pyrimidin-2-one **70** and **291** with 30% hydrogen peroxide in acetic acid at 100°C gave 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline **292** in good yield (80CPB3537).

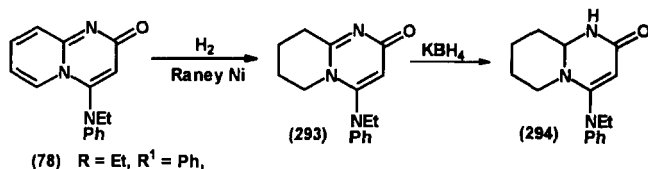
Oxidation of 4-methoxy-3-(3-methyl-2-butenyl)-2*H*-pyrido[1,2-*a*]pyrimidin-2-one gave the 3-(3-methyl-2,3-dihydroxybutyl) derivative (89MI16).



The hydrolysis of compound **291** did not occur in aqueous acetic acid to yield compound **70** (80CPB3537).

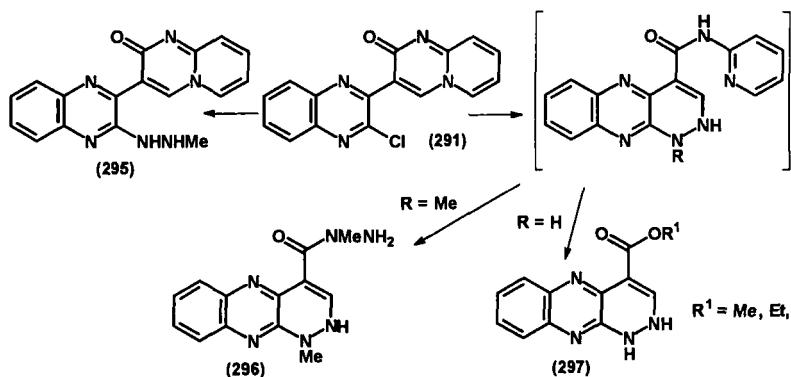
Catalytic reduction of 2*H*-pyrido[1,2-*a*]pyrimidin-2-one **78** (R = Et, R<sup>1</sup> = Ph) with hydrogen over Raney nickel in ethanol at ambient tempera-

ture gave 6,7,8,9-tetrahydro derivative **293**. The C=N double bond of tetrahydropyridopyrimidin-2-one **293** was reduced with potassium borohydride in an aqueous solution at 35°C to give hexahydropyridopyrimidin-2-one **294** (88FES705).

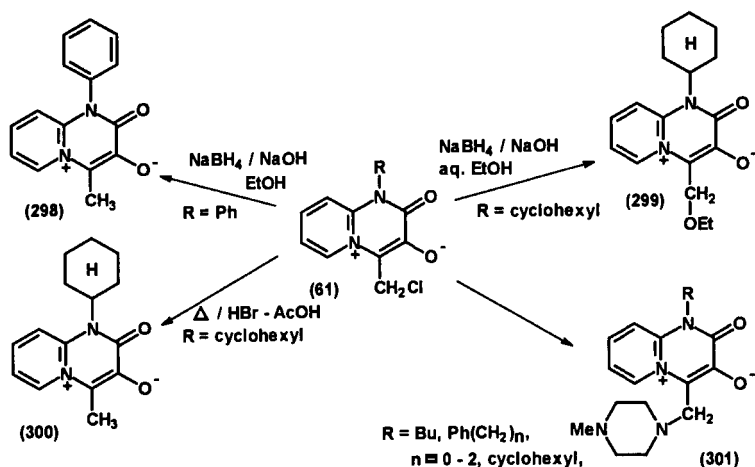


Chloro derivative **291** was obtained from dioxo derivative **70** by treatment of phosphoryl chloride in dimethylformamide at 100°C for 2 hours (80CPB3537). The treatment of chloro derivative **291** with methylhydrazine in a mixture of ethanol and chloroform under reflux gave 2*H*-pyrido[1,2-*a*]pyrimidin-2-one **295** and rearranged pyridazino[3,4-*b*]-quinoxaline **296** in 4.8% and 78% yields, respectively (Scheme 21) (80CPB3537). 3,4-Dihydroquinoxalinone **70** could not be rearranged into pyridazino[3,4-*b*]quinoxaline **296** by treatment with methylhydrazine. When hydrazine hydrate was employed instead of methylhydrazine, tricyclic ethyl ester **297** ( $R^1 = Et$ ) was obtained. The latter reaction gave methyl ester **297** ( $R^1 = Me$ ) when carried out in a mixture of methanol and chloroform (80CPB3537).

Reduction of 4-chloromethyl-1-phenyl-2-oxopyrido[1,2-*a*]pyrimidin-5-ium-3-olate **61** ( $R = Ph$ ) with sodium borohydride in the presence of 4 drops of 25% aqueous solution of sodium hydroxide at 50°C for 9 hours, then at reflux for 2 hours afforded 4-methyl derivative **298** in 26% yield and 28% of 2-anilinopyridine (Scheme 22) (89CCC1376). When 1-cyclohexyl



SCHEME 21



SCHEME 22

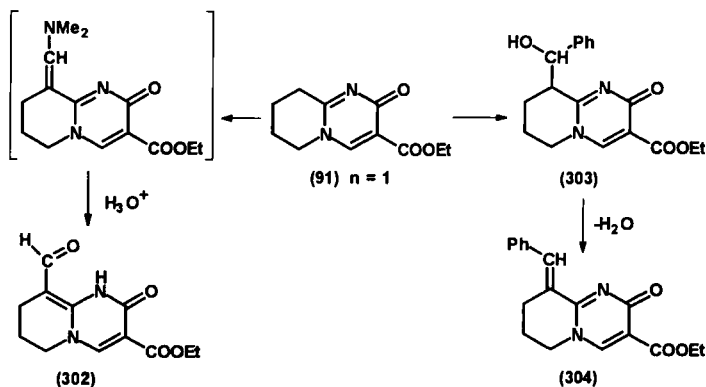
derivative **61** (R = cyclohexyl) was treated with a mixture of sodium borohydride and sodium hydroxide at 65°C for 6 hours, then at reflux for 20 minutes, only 4-ethoxymethyl derivative **299** could be isolated from the complex reaction mixture in 10% yield. Heating 4-chloromethyl-1-cyclohexyl derivative **61** (R = cyclohexyl) in acetic acid containing 36% hydrogen bromide at 110°C for 8.5 hours afforded 4-methyl derivative **300** in 28% yield—probably a product of disproportionation. Reaction of 1-methylpiperazine with 4-chloromethylpyrido[1,2-*a*]pyrimidin-5-ium-3-olates **61** in chloroform at 50°C for 2.5 hours gave 4-(4-methylpiperazino) methyl derivatives **301** (89CCC1376; 91CZP264950). The products **298–301** were characterized by UV, IR, <sup>1</sup>H and <sup>13</sup>C NMR, and mass spectra.

Unlike 2-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, 4-amino-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones did not react with a Vielsmeier–Haack reagent consisting of a mixture of phosphoryl chloride and dimethylformamide at 90°C for 8 hours or at 140°C for 90 minutes (87JHC329).

Ethyl 2-oxo-6,7,8,9-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **91** (*n* = 1) contains a reactive methylene group at position 9, which reacted easily with electrophiles (82JHC909).

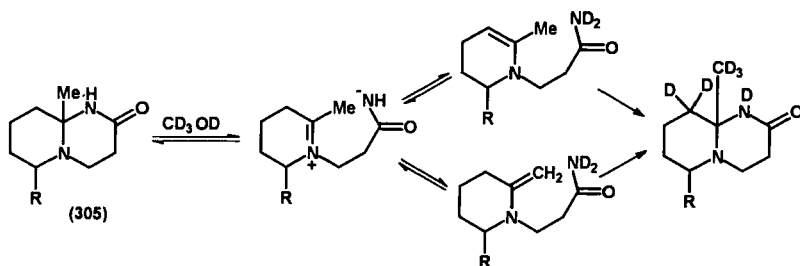
Vielsmeier–Haack formylation of 2-oxotetrahydropyridopyrimidine-3-carboxylate **91** (*n* = 1) with a mixture of phosphoryl chloride and dimethylformamide afforded 9-formyl derivative **302** after hydrolytic work-up [85JCS(P2)1873]. The predominant tautomeric form of the formyl derivative is the 1,6,7,8-tetrahydro form.

2-Oxotetrahydropyridopyrimidine **91** (*n* = 1) was left to react with



benzaldehyde in a melt at ambient temperature for 30 minutes, then diluted with ethanol. When the solution was allowed to stand for 1 month at 0–5°C, an addition product **303** could be isolated (89JHC1061). When the reaction was carried out in boiling benzene in the presence of a few drops of concentrated hydrochloric acid, condensation product **304** with *Z* geometry was obtained. Under these conditions the addition product **303** could also be converted into the condensation product **304**.

Perhydropyrido[1,2-*a*]pyrimidin-2-one **305** exhibits prototropic equilibrium and ring-chain tautomerism (92AP177). In methanol- $\text{d}_4$  hexadeuterated bicyclic compounds were formed.

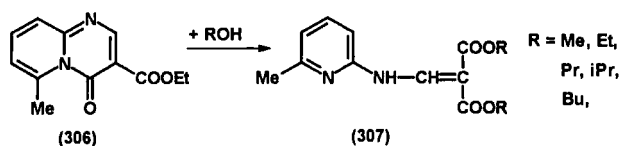


### C. 4-Oxo-4*H*-PYRIDO[1,2-*a*]PYRIMIDINES

#### 1. Hydrolysis, Solvolysis, and Stability

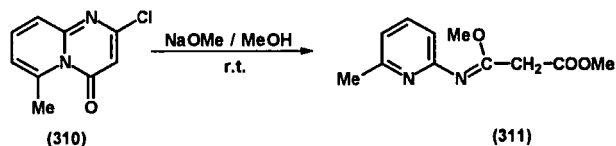
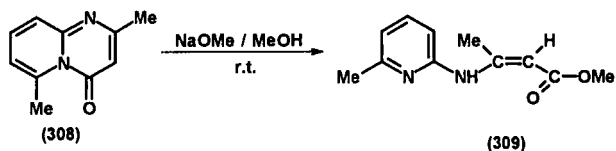
Dialkyl [*N*-(6-methyl-2-pyridyl)amino]methylenemalonates **307** were obtained when ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **306** were heated in benzene with an alcohol in the presence of concentrated sulfuric acid at 75–80°C (84MIP1).



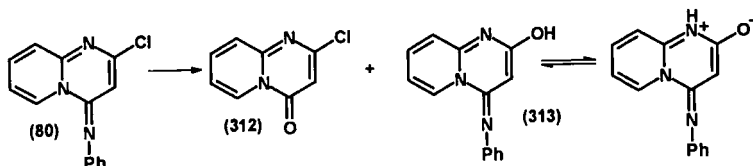


Ring cleavage occurred during the saponification of ethyl 9-benzyloxy- and 9-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates (89TL1529).

The treatment of 2-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **308** and **310** with sodium methylate for 2 hours gave ring-opened products **309** and **311** (86JHC1295). The ring cleavage of compound **310** was accompanied by chloro-to-methoxy exchange. Under similar conditions the 6-desmethyl derivative compound **310** did not suffer ring opening; only the chloro atom was substituted by the methoxy group.

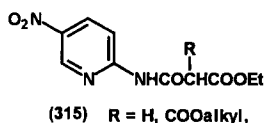
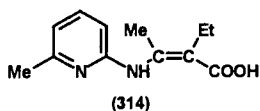


Heating 2-chloro-4-phenylimino-4*H*-pyrido[1,2-*a*]pyrimidine **80** in 6*N* aqueous hydrogen chloride under reflux for 30 minutes afforded a mixture of 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **312** and 2-hydroxy-4-phenylimino-4*H*-pyrido[1,2-*a*]pyrimidine **313** in 10% and 24% yields, respectively (87JHC329).

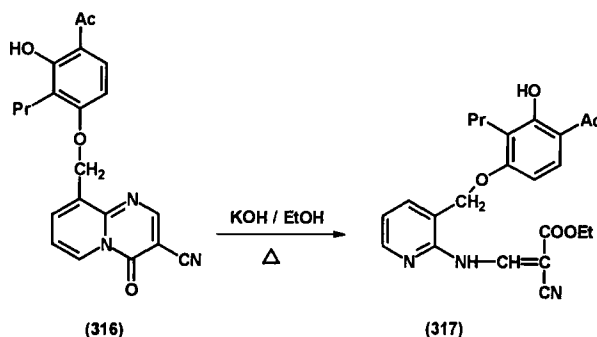


The thermostability of the hydrochloride salt of 3-ethyl-2,6-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (Chinoin-150) in aqueous solution was investigated (85MI4). Chinoin-150 was fairly stable in acidic medium, but a slow decomposition was observed at pH 7.4 and 9. At pH 12 nearly quantitative decomposition was detected after 11 days at 90°C. From the aqueous solution the ring-opened product **314** was isolated (87MI1).

When 7-nitro-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **119** ( $R = \text{NO}_2$ ,  $R^1 = \text{H}$ ) was boiled in an alcohol for 15 minutes, it was partly converted to diesters **315** ( $R = \text{COOalkyl}$ ) (92AJC1825). If the 7-nitro derivative was heated in hexachloroacetone or in dimethyl sulfoxide, malonamate **315** ( $R = \text{H}$ ) was formed, presumably due to traces of adventitious water.

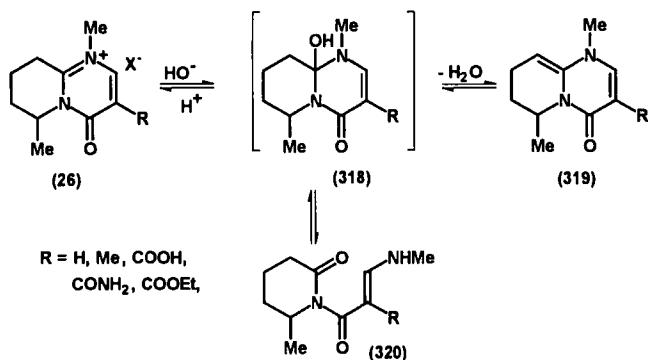


Heating 9-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile **316** in 1 *N* potassium hydroxide ethanolic solution at 40–60°C afforded 2-pyridylaminomethylenecyanoacetate **317** [91JAP(K)197461].

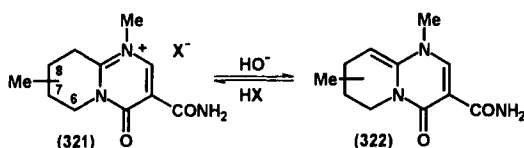


1,6-Dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidinium salts **26** undergo a characteristic transformation, leading via the pseudobases **318** to the 1,6-dimethyl-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **319** or the ring-opened aminocarbonyl tautomers **320** in aqueous alkaline medium (Scheme 23) (86ACH135). The equilibrium was shifted to the enamino form **319** when  $R$  was an ester and to the aminocarbonyl form **320** when  $R$  was a hydrogen atom or a methyl group. Each form was characterized by UV and  $^1\text{H}$  NMR spectra, and the aminocarbonyl forms by  $^{13}\text{C}$  NMR spectra. In the case of the ethyl ester **26** ( $R = \text{COOEt}$ ), both the enamine **319** ( $R = \text{COOEt}$ ) and aminocarbonyl forms **320** ( $R = \text{COOEt}$ ) could be isolated. The aminocarbonyl form **320** ( $R = \text{COOEt}$ ) cyclized rapidly to enamine **319** ( $R = \text{COOEt}$ ) in water.

3-Carbamoyl-1,6-, -1,7-, and -1,8-dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidinium methyl sulfates **321** ( $X = \text{MeSO}_4$ ) were converted to chlorides **321** ( $X = \text{Cl}$ ) via enamino forms **322** (85JOC2918).

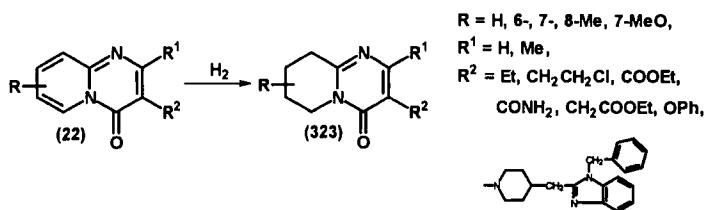


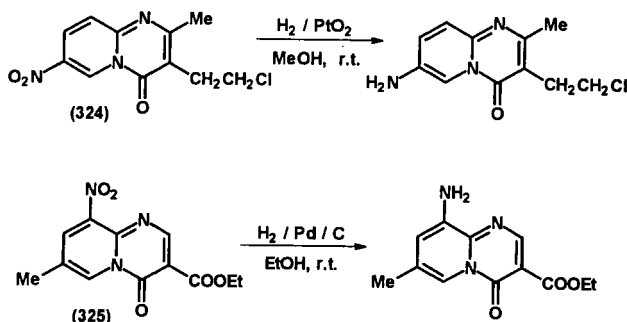
SCHEME 23



## 2. Hydrogenation, Reduction, and Oxidation

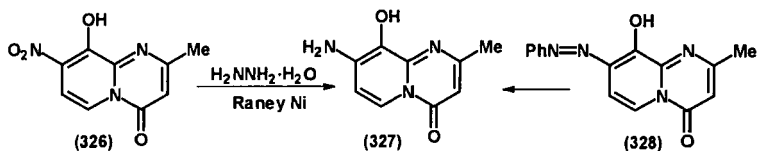
The pyridine moiety of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **22** could be generally saturated by catalytic hydrogenation over palladium-on-charcoal (81USP4291036; 82MI6; 83H1083, 83JMC1126; 85EUP144101, 85EUP151826; 86JOC394; 87USP4695575; 90EUP368388; 92USP5158952) or Raney nickel (81USP4291036; 93FES1225) at atmospheric pressure as well as under pressure at room temperature in acetic acid (e.g., 83JMC1126), in an alcohol or mixture of alcohols (e.g., 85EUP144101), or in the absence or presence of hydrogen chloride (e.g., 85EUP144101) to give 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **323**. If the pyridine ring bears a nitro group (e.g., **324** and **325**), only the reduction of the nitro group occurs, without saturation of the pyridine ring of pyrido[1,2-*a*]pyrimidin-4-one (84EUP110435; 91H1455).





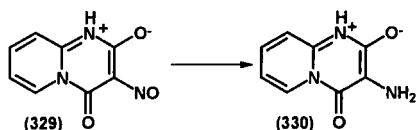
Reduction of nitro derivatives of 2-hydroxy-4-oxo-pyrido[1,2-*a*]pyrimidine-3-carboxylates **119** ( $\text{R} = \text{NO}_2$ ,  $\text{R}^1 = \text{H}$ ;  $\text{R} = \text{H}$ ,  $\text{R}^1 = \text{NO}_2$ ) could be carried out by zinc and acetic acid to yield the appropriate unsaturated amino derivative (92AJC1825). Catalytic reduction at 1 atm gave only partially reduced products.

Heating 9-hydroxy-2-methyl-8-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **326** in dimethylformamide in the presence of hydrazine hydrate and Raney nickel at 50°C afforded 8-amino derivative **327** (92KGS1660). 8-Amino derivative **327** was also prepared from 8-phenylazo derivative **328**.



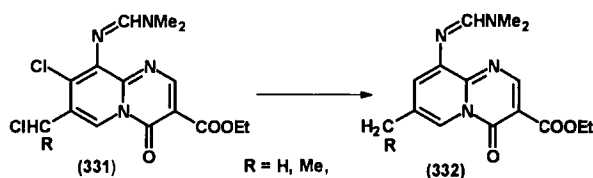
Chemical reduction [with aqueous titanium(III) chloride in dilute acetic acid] or catalytic reduction (in the presence of 10% palladium-on-charcoal by transfer hydrogenation from cyclohexene or with hydrogen) of 3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **176** ( $\text{R} = \text{H}$ , 8-Me, 8-OMe, 7-Cl) gave 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [90JCR(S)308]. Chemical and catalytic reduction of 3,8-dinitro-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one yielded an unstable product.

Reduction of 3-nitroso derivative **329** by treatment with activated zinc dust in boiling acetic acid for 6 hours gave 3-amino derivative **330** [91IJC(B)839]. 2,3-Diamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was pre-



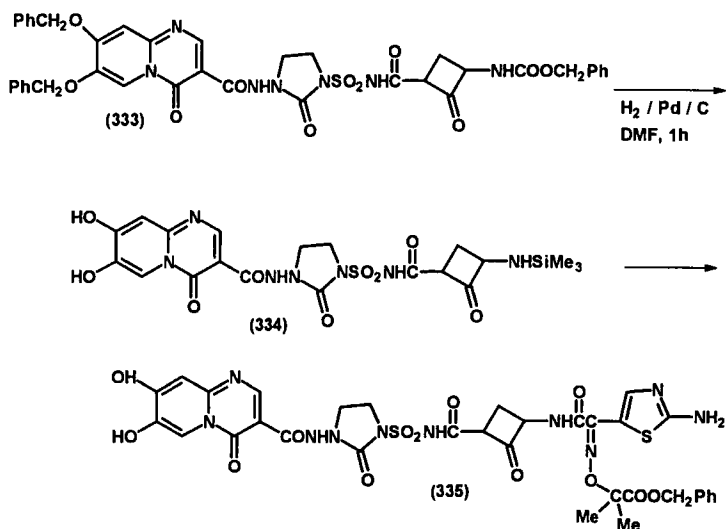
pared by the reduction of 2-amino-3-nitroso-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with a mixture of disodium sulfide and ammonium chloride in 80% ethanol at reflux for 2 hours (92M123).

Catalytic reduction of 7-(1-chloroalkyl)-8-chloro-9-[(dimethylaminomethylene)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **331** over 10% palladium-on-charcoal with hydrogen in acetic acid gave 7-alkyl-9-[(dimethylaminomethylene)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **332** (91H1455).



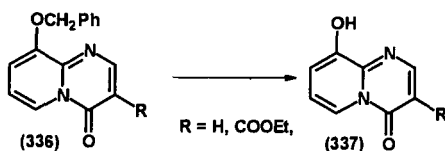
Depending upon the reaction conditions, selective debenzoylation or debenzoylation and saturation of the pyridine moiety of benzyloxy derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **333**, **336** and **338** could be carried out by catalytic hydrogenation over palladium-on-charcoal.

7,8-Dihydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **334** was obtained, when dibenzyloxy derivatives **333** were hydrogenated in dimethylformamide in the presence of *N*-methyl-*N*-trimethylsilyl trifluoroacetamide. Dihydroxypyrido[1,2-*a*]pyrimidin-4-one **334** was then reacted, without isolation, with (*Z*)-2-amino- $\alpha$ -[(2-diphenylmethoxy)-1,1-dimethyl-2-oxoe-

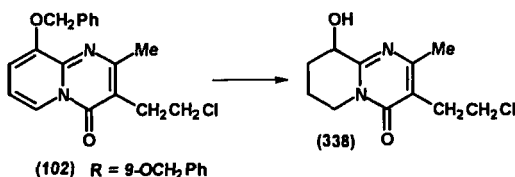


thoxy]imino-4-thiazoleacetic acid 1-benzotriazole ester to give pyridopyrimidinone derivative **335** (88USP4777252).

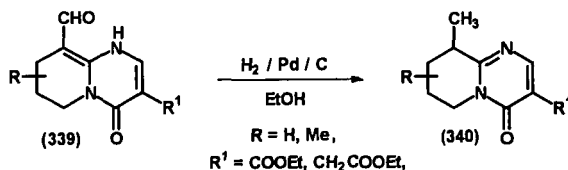
Hydrogenolysis of the benzyl group of 9-benzyloxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **336** in ethanol over 10% palladium-on-charcoal under pressure of hydrogen (3 atm), or in the presence of cyclohexene and 10% palladium hydroxide, afforded 9-hydroxy derivatives **337** in 25–30% and 78% yield, respectively (89TL1529; 91JHC1287).



9-Hydroxy-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **338** was obtained when the 9-benzyloxy derivative **102** ( $\text{R} = 9\text{-OCH}_2\text{Ph}$ ) was hydrogenated in methanol over 10% palladium-on-charcoal under normal pressure at ambient temperature (90EUP368388; 92USP5158952).

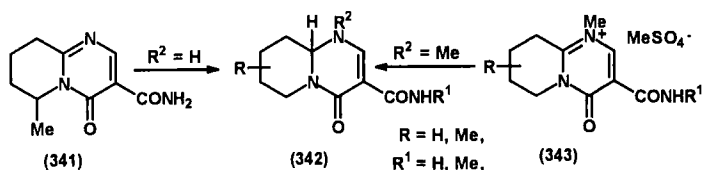


9-Methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **340** were also prepared from 9-formyl-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **339** by catalytic hydrogenation in acidified ethanol over palladium-on-charcoal (83JMC1126; 86JOC394).

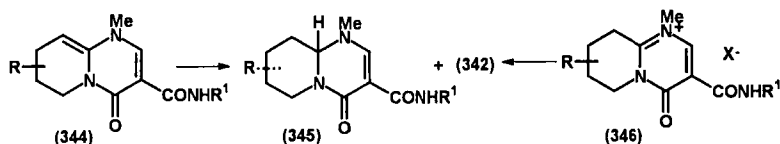


Catalytic hydrogenation of 9-benzylidene-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates (89JHC1061) or 9-benzylidene-2-methyl-3-(2-chloroethyl)-6,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (91EUP453042) in alcohol over palladium-on-charcoal under atmospheric pressure at room temperature gave 9-substituted 6,7,8,9-tetrahydro derivatives.

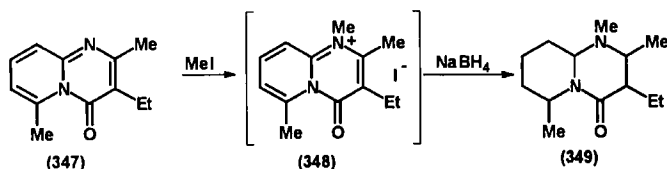
Reduction of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **341** and their quaternary salts **343** with sodium borohydride in water and methanol yielded the thermodynamically stable epimer **342** of 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (83SZP635100; 85JOC2918),



while catalytic reduction of 6- or 7-methyl derivatives of the quaternary salts **346** or 1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **344** gave diastereomeric mixtures of hexahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **342** ( $R^2 = Me$ ) and **345** over palladium-on-charcoal (85JOC2918). In the case of 6-methyl derivatives, the epimers **345** ( $R = 6-Me$ ;  $R^1 = H, Me$ ) were separated by fractional crystallization. The  $C=N$  double bond of 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide **341** and that of its optically active enantiomers was saturated by treatment with sodium borohydride in water at 10°C (85JOC2918).

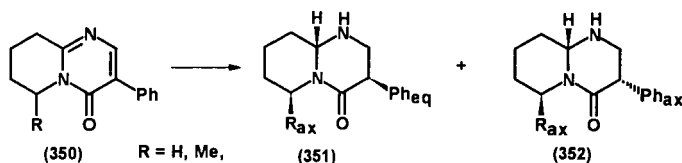


Perhydropyrido[1,2-*a*]pyrimidin-4-one **349** was prepared by first reacting pyrido[1,2-*a*]pyrimidin-4-one **347** with methyl iodide in acetone in a sealed tube at 150°C for 24 hours, then dissolving the evaporated residue in methanol, and treating the methanolic solution with sodium borohydride (81USP4291036). Perhydro derivative **349** was isolated as its hydrochloride salt. The stereochemistry of the product was not determined.



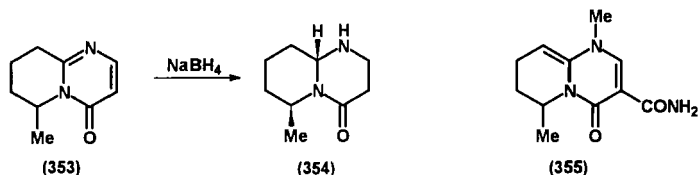
Catalytic reduction of 3-phenyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **350** over platinum oxide at 30°C under pressure of

62 atm afforded a diastereomeric mixture of perhydro derivatives **351** and **352**, which could be separated by fractional crystallization (82JOC4780). The conformational analysis of the perhydropyridopyrimidinones **351** and **352** was carried out by  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR spectroscopy. A slow epimerization through oxo-enol tautomerism, between **351** and **352** was observed in ethanolic solution.

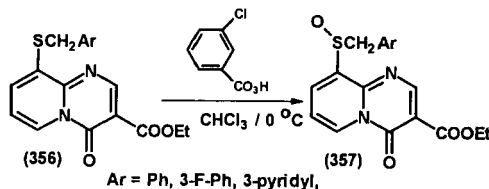


Reduction of 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **353** with sodium borohydride in water at  $0^\circ\text{C}$  yielded perhydropyridopyrimidinone **354** (82JOC4780).

The stability of Chinoin-127 (**19**) was investigated in the solid state and in aqueous solutions (83MI11; 85MI20). By means of TLC the formation of an oxidation product, 1,6-dimethyl-1,6,7,8-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide **355**, could be detected.



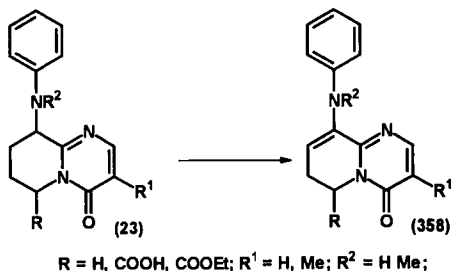
Oxidation of 9-aralkylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **356** with *m*-chloroperbenzoic acid afforded 9-aralkylsulfinyl derivatives **357** (87EUP218423). Oxidation of 2-methoxy-3-(3-methyl-2-butenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one gave the 3-(3-methyl-2,3-dihydroxybutyl) derivative (89MI16).



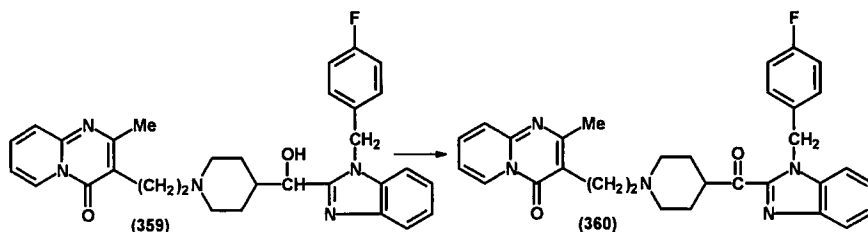
9-Amino-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **23** ( $\text{R}^1 = \text{H, COOEt}$ ) and 3-carboxylic acids **23** ( $\text{R}^1 = \text{COOH}$ ) were oxi-



dized to 6,7-dihydro derivatives **358** when air was bubbled into a chloroform solution at ambient temperature or at reflux or into 2% aqueous sodium hydroxide solutions (83JMC1494; 85JHC1253). Autooxidation is most probably a free-radical chain process with ground-state triplet oxygen.



The side-chain hydroxy group of pyrido[1,2-*a*]pyrimidin-4-one **359** was oxidized by manganese (IV) oxide in dichloromethane at ambient temperature for 90 hours to give oxo derivative **360** (92MIP3).

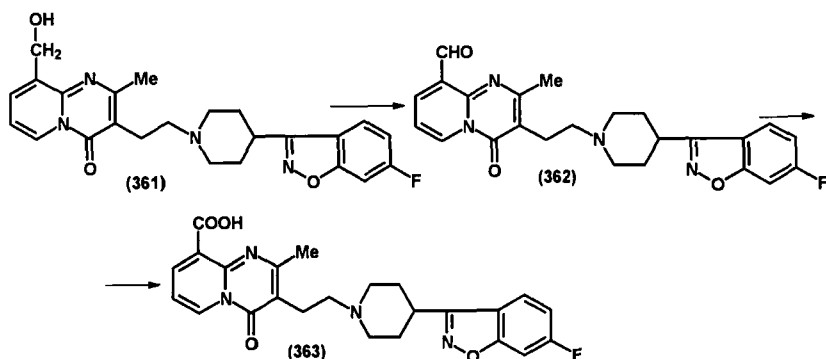


9-Formyl derivative **362** was prepared when 9-hydroxymethylpyrido-pyrimidin-4-one **361** in dichloromethane was added to a cooled mixture of oxalyl chloride and dimethyl sulfoxide at  $-50^{\circ}\text{C}/-60^{\circ}\text{C}$  in the presence of triethylamine. 9-Formyl derivative **362** was oxidized with silver nitrate in aqueous ethanol, and after 15 minutes of stirring the reaction mixture was treated with aqueous potassium nitrate for 2 hours at ambient temperature to give pyrido[1,2-*a*]pyrimidine-9-carboxylic acid **363** (91EUP453042).

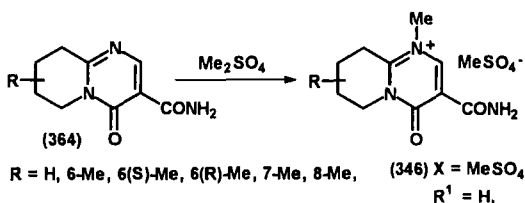
### 3. Quaternization, Alkylation, and Acylation

3-Ethyl-1,2,6-trimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium iodide **348** was obtained from pyrido[1,2-*a*]pyrimidinone **347** with methyl iodide in acetone in a sealed tube at  $150^{\circ}\text{C}$  for 24 hours (81USP4291036).

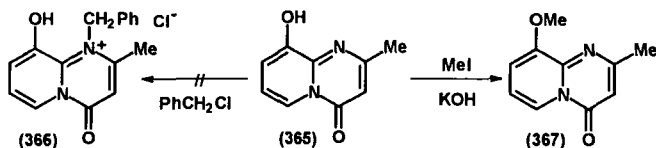
Quaternary salts of 6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimi-



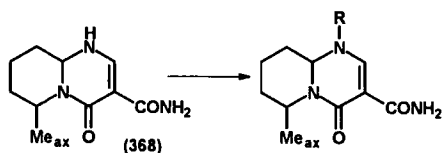
dine-3-carboxamides **346** ( $X = \text{MeSO}_4$ ,  $R^1 = \text{H}$ ) were obtained from tetrahydropyridopyrimidine-3-carboxamides **364** by treatment with dimethyl sulfate in boiling nitromethane for 5 hours (85JOC2918). The 9-methyl derivative could not be transformed to the quaternary salt, probably because of the steric hinderance of the 9-methyl group on position 1.



The quaternary salt **366** was not obtained from 9-hydroxyl-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **365** and benzyl chloride by heating in nitromethane (92KGS1660). The hydroxy group of 9-hydroxylpyridopyrimidin-4-one **365** was alkylated with methyl iodide in dimethyl sulfoxide at 40°C for 30 hours to give 9-methoxy derivative **367** in 9% yield.



*N*(1)-Alkylation of 1,6,7,8,9,9a-hexahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide **368** was carried out with dialkyl sulfate in water in the presence of sodium hydroxide, with triethyl phosphate in the presence of potassium carbonate at 235°C, and with butyl bromide in boiling ethanol in the presence of potassium carbonate for 30 hours (83SZP635101; 85JOC2918).



The amino group of 2-amino-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was acylated with chloroacetyl chloride in benzene at ambient temperature to give 2-(chloroacetyl-amino)-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (92MI23).

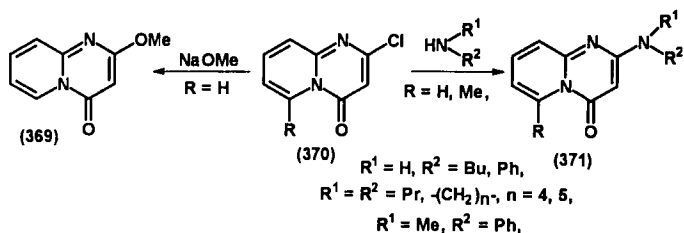
Some further reactions are mentioned in Sections, IV,C,4; IV,C,5; IV,C,8; and IV,C,9.

#### 4. Reactions Involving the C-2 Atom or the 2-Substituent of Pyrido[1,2-*a*]pyrimidin-4-ones

2-Chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **370** ( $R = H$ ) was obtained in the reaction of malonyl- $\alpha$ -aminopyridine **37** and phosphoryl chloride at 100°C (92MI23).

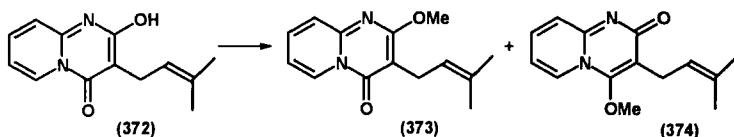
The halogen atom at position 2 of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **370** easily reacts with *N*- and *O*-nucleophiles to yield 2-amino- and 2-alkoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (82FES747; 86JHC1295; 87JHC329; 92FES77, 92JHC25).

2-Methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **369** could be prepared from a 2-chloro derivative **370** ( $R = H$ ) with sodium methylate in methanol at ambient temperature, while a similar reaction of 6-methyl derivative **370** ( $R = Me$ ) led to the formation of a ring-opened product (86JHC1295) (see also Section IV,C,1).

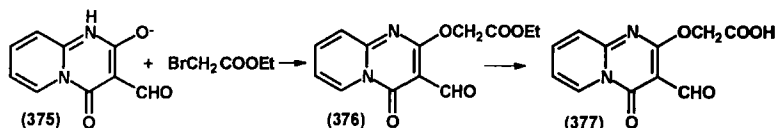


Methylation of 2-hydroxy-3-(3-methyl-2-butenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **372** afforded a mixture of 2-methoxy-4-oxo-4*H*- **373** and 4-methoxy-2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine **374** (89MI16).

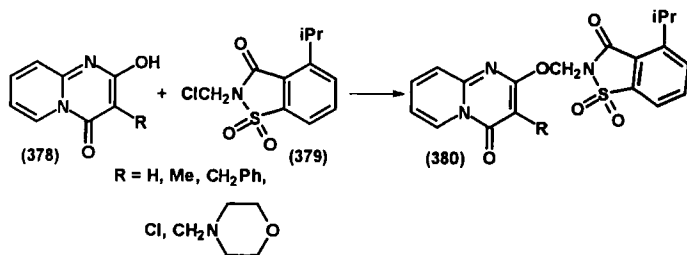
Reaction of 3-formyl derivative **375** with ethyl bromoacetate in boiling ethanol in the presence of sodium ethylate yielded 2-[(ethoxycarbonyl)methoxy]-3-formylpyrido[1,2-*a*]pyrimidin-4-one **376** [91IJC(B)839]. The



ester group of compound **376** was hydrolyzed in refluxing concentrated hydrochloric acid to give carboxylic acid derivative **377**.



The 2-hydroxyl group of 3-[4-(2-cyanophenyl)phenyl]-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were alkylated with various alkyl bromides (94MI2). *O*-Alkylation of 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **378** with 2-chloromethyl-4-isopropyl-6-methoxysaccharine **379** in dimethylformamide in the presence of potassium *tert*-butoxide or sodium hydride for 1 hour or for 2.5 days, or in a mixture of methanol and dimethylformamide in the presence of cesium carbonate for 2 days at room temperature, gave proteolytic enzyme inhibitor pyridopyrimidinones **380** (93EUP547708).



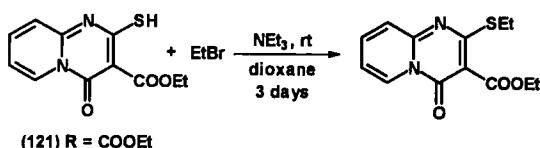
Reaction of 2-chloropyridopyrimidin-4-one **370** (R = H) and its 3-formyl derivative with excess ammonium acetate at 180°C for 5 minutes, then at 210°C for 3 minutes, gave 2-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (92MI23). The 2-chloro derivatives **370** reacted with primary and secondary amines (e.g., butylamine, dipropylamine, pyrrolidine) in boiling ethanol for 4–10 hours (82FES747; 83FES1225; 86JHC1295; 92FES77), with piperidine in boiling dioxane for 20 minutes (86JHC1295), with aromatic amines in ethylene glycol at 160°C for 4 hours (87JHC329), or in a melt at 200°C (93FES1225) to afford (2-substituted/amino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **371**, generally in good yields.

When ethyl 2-chloro-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylate

was reacted with butylamine or piperidine in boiling ethanol for 3 hours, the appropriate 2-amino derivative was obtained (92JHC559).

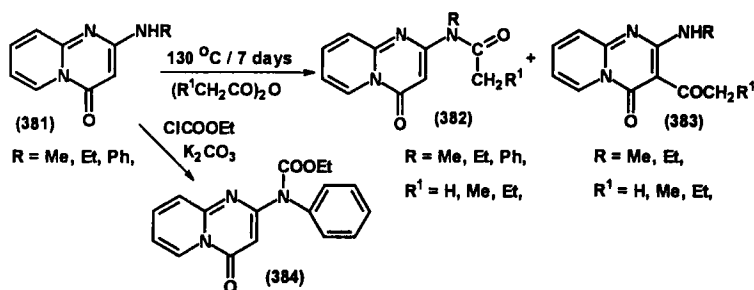
2-Alkylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **371** ( $R = R^2 = H$ ;  $R^1 = Me, Et$ ) were prepared when 2-chloro derivative **370** ( $R = H$ ) reacted with methylamine hydrochloride or ethylamine hydrochloride in boiling ethanol for 24 hours in the presence of triethylamine (92JHC25).

The 2-mercapto group of pyridopyrimidinone **121** ( $R = COOEt$ ) was alkylated with ethyl bromide (81CCC2428).



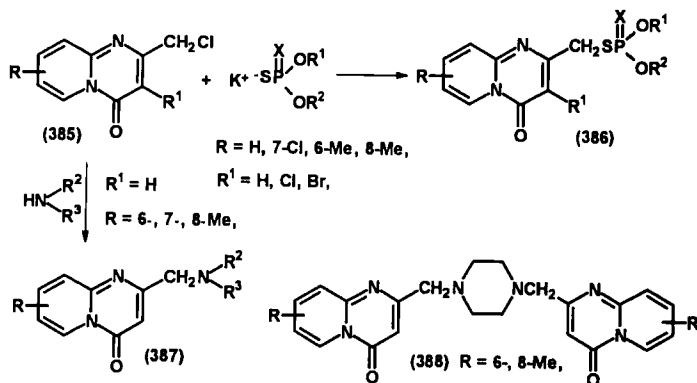
Different 2-amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitriles were obtained in the reaction of 2-methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitriles with cyclic amines and hydrazine (91MI17). The amino moiety of the 2-hydrazino group was condensed with different aromatic aldehydes.

Acylation of 2-(alkylamino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **381** ( $R = Me, Et$ ) in excess anhydride gave 2-acylamidopyrido[1,2-*a*]pyrimidin-4-ones **382** and 3-acyl-2-(alkylamino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **383** in 76–97% and 1.1–7.2% yields, respectively (92JHC25). 2-Phenylamino derivative **381** ( $R = Ph$ ) afforded only 2-acylamido derivatives **382** ( $R = Ph$ ;  $R^1 = H, Et$ ). Reaction of 2-phenylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **381** ( $R = Ph$ ) with ethyl chloroformate in toluene at 130°C for 18 hours in the presence of potassium carbonate gave 2-(*N*-ethoxycarbonyl-*N*-phenyl)amino derivative **384**.



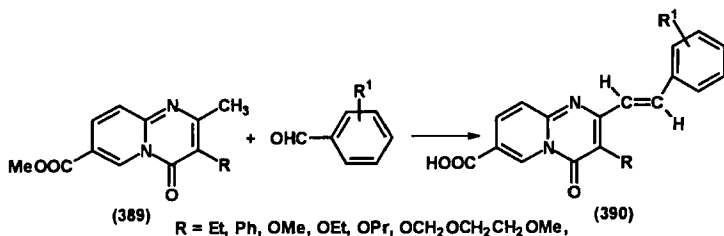
Reaction of 2-chloromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **385** with *O,O*-dialkyl phosphorothioates and phosphorodithioates in a mixture of ethanol and toluene in the presence of potassium hydroxide at 60–70°C gave insecticidal or nematocidal phosphorus derivative **386** (83EUP81945).

2-Aminomethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **387** were obtained in the reaction of 2-chloromethyl derivatives **385** ( $R^1 = H$ ) and cyclic or disubstituted amines in boiling toluene in the presence of triethylamine for 24 hours (86FES926). When 1 mole of piperazine was reacted with



2 moles of 2-chloromethyl derivatives **385** ( $R = 6-, 8\text{-Me}$ ) bis products **388** were prepared. In the reaction of 2-chloromethyl-6-methylpyrido-pyrimidin-4-one **385** ( $R = 6\text{-Me}, R^1 = H$ ) and formylpiperazine a 4:1 mixture of compound **387** ( $R = 6\text{-Me}, R^2 = R^3 = CH_2CH_2NCH_2CH_2$ ) and bis product **388** ( $R = 6\text{-Me}$ ) was obtained. The formyl group of 2-[(4-formylpiperazino)methyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was hydrolyzed by heating in hydrochloric acid for 2 hours. The free NH group of 2-piperazinomethyl-7- and -8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was acylated by 2-furoylchloride in pyridine at room temperature.

Aromatic aldehydes were condensed with the 2-methyl group of 4-oxypyrido[1,2-*a*]pyrimidine-7-carboxylates **389** in boiling methanol in the presence of sodium methylate for 20–96 hours to give 2-*trans* isomers **390** (83MI12; 84FES837). Ester hydrolysis also occurred and 7-carboxylic acids **390** were obtained. Condensation did not occur when the pyrido[1,2-*a*]pyrimidin-4-one **389** ( $R = OH$ ) contained a free hydroxyl group at position 3 (84FES837).



When 2,4-dioxypyrido[1,2-*a*]pyrimidines **391** were treated dropwise in acetonitrile with tetrachlorosilane in 1,2-dichloroethane in the presence of sodium iodide at room temperature, 2-acetamido-3,4-dihydro-2*H*-pyridopyrimidin-4-ones **396** were obtained after work-up [92MJ24; 93IJC(B)637]. In the first step iodotrichlorosilane was formed, and 1,2-addition of iodotrichlorosilane to a 2-carbonyl group of pyridopyrimidine **391** led to the formation of  $\alpha$ -iodosilyl esters **392**, which reacted with acetonitrile. After the rearrangement of adduct **393** and a further reaction with a second mole of iodotrichlorosilane, the hydrolysis of disilylated intermediates **395** yielded 2-acetamido-3,4-dihydro-2*H*-pyridopyrimidin-4-ones **396** (see Scheme 24).

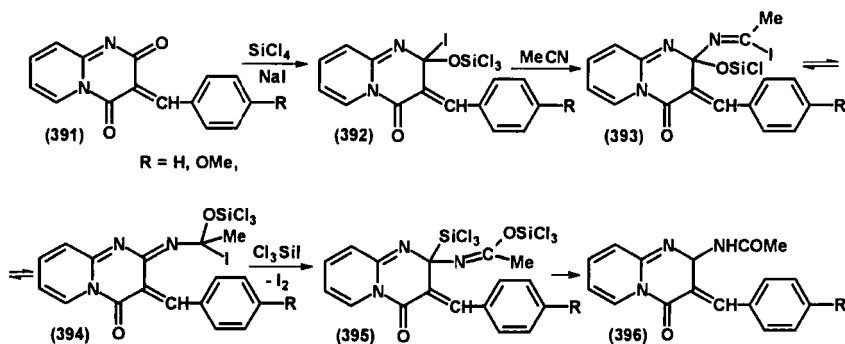
### 5. Reactions Involving the C-3 Atom or the 3-Substituent of Pyrido[1,2-*a*]pyrimidin-4-ones

Electrophilic substitutions occur easily at position 3 of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

Nitrosation of "malonyl- $\alpha$ -aminopyridine" (**37**) in 2 *N* hydrochloric acid at 0°C with a 1 *N* aqueous sodium nitrite afforded the 3-nitroso derivative **329** [91IJC(B)839]. 2-Amino-3-nitroso-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared from 2-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one by treatment of 1 *N* sodium nitrite in 2 *N* hydrochloric acid at 0°C for 30 minutes (92MI23).

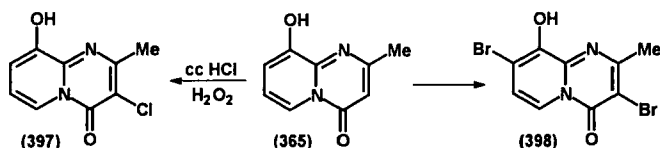
3-Nitro-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared from 6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one by nitration with a mixture of concentrated nitric and sulfuric acids at ambient temperature for 2 hours (85JHC481).

Chlorination of 9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **365** with concentrated hydrochloric acid in the presence of a 15% aqueous

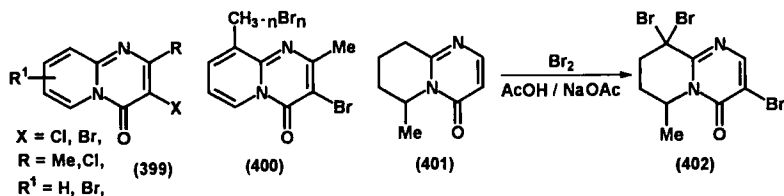


SCHEME 24

solution of hydrogen peroxide at 100°C gave 9-hydroxy-3-chloro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **397** (92KGS1660). Bromination of 9-hydroxy derivative **365** with dioxane dibromide in acetic acid for 1 hour afforded 3,8-dibromo-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **398**. 3-Bromo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **399** (X = Br) were



obtained from the appropriate 3-unsubstituted derivatives with bromine in chloroform at room temperature (85JHC481), or with *N*-bromosuccinimide (NBS) in carbon tetrachloride in the presence of dibenzoyl peroxide [84IJC(B)1117]. Besides nuclear bromination, side-chain bromination also occurred in the case of 2,9-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one to afford a mixture of the 3-bromo derivative **399** (R = Me, R<sup>1</sup> = 9-Me, X = Br) and the 9-bromomethyl- and 9,9-dibromomethyl derivatives **400** (*n* = 1, 2) in 73%, in 9%, and 9% yields, respectively, when bromination was carried out with NBS [84IJC(B)1117]. When 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **401** was brominated with bromine in acetic acid in the presence of sodium acetate at 50–60°C, 3,9,9-tribromo compound **402** was obtained (83OMR687).



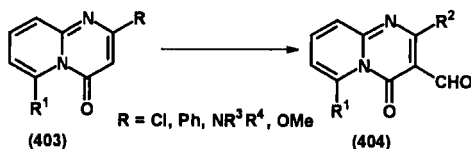
3-Chloropyrido[1,2-*a*]pyrimidin-4-ones **399** (R = Me, Cl; R<sup>1</sup> = 6-Me; X = Cl) were prepared in excellent yields when 3-unsubstituted derivatives reacted with phosphorus pentachloride in phosphoryl chloride at 105–110°C for 1.5 hours (85JHC481). Other 3-bromo- and 3-chloro-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were also prepared from 3-unsaturated derivatives with halogenation agents (e.g., with *N*-chlorosuccinimide (NCS) in a mixture of carbon tetrachloride and ethyl acetate) (83EUP81945).

“Malonyl- $\alpha$ -aminopyridine” (**37**) reacted with aryldiazonium chloride in ethanol in the presence of sodium acetate to give 3-arylhydrazono-2,4-dioxypyrido[1,2-*a*]pyrimidines (89MI6). Heating compound **37** in for-

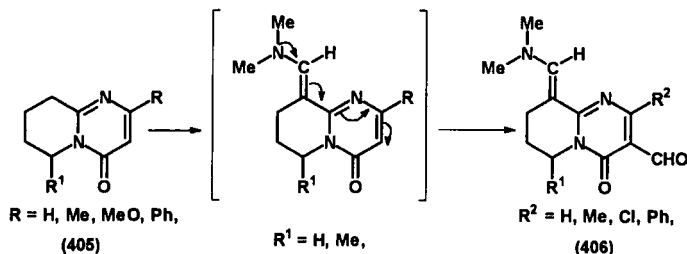


mamide at 210°C for 2 hours gave 3-formyl derivative **375** [91IJC(B)839]. When 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **370** ( $R = H$ ) was heated in formamide at 180°C for 15 minutes, and then at 210°C for 5 minutes, 2-chloro-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained in 65% yield (92MI23).

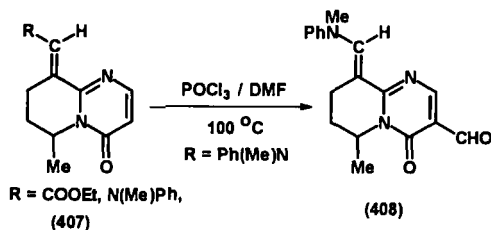
Vielsmeier-Haack formylation of 3-unsubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **403** by a mixture of phosphoryl chloride and dimethylformamide at ambient temperature for 30 minutes, then 95°C for 60–90 minutes afforded 3-formyl derivatives **404** (86JHC1295; 87JHC329; 93FES1225). Under these conditions 2-(butylamino) derivatives **403** ( $R = NHBu$ ,  $R^1 = H, Me$ ) yielded 2-(*N*-formyl-*N*-butylamino)-3-formyl compound **404** [ $R^1 = H, Me$ ;  $R^2 = N(CHO)Bu$ ] while 2-methoxypyridopyrimidinone **404** ( $R = OMe$ ,  $R^1 = H$ ) gave 2-chloro-3-formyl derivative **404** ( $R^1 = H$ ,  $R^2 = Cl$ ). When the latter reactions were carried out at 15–35°C, substituents at position 2 were not involved in the reaction and 2-butylamino-3-formyl and 2-methoxy-3-formylpyridopyrimidin-4-ones **404** ( $R^2 = NHBu, MeO$ ) were isolated (86JHC1295). Formylation did not occur with 2-unsubstituted or 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**403**,  $R = H$  or  $Me$ ) (86JHC1295).



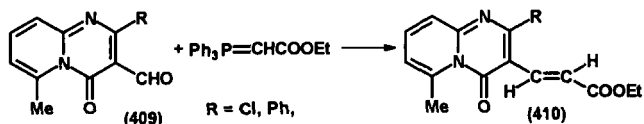
Formylation of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **405** with a mixture of phosphoryl chloride and dimethylformamide at 15–20°C for 0.5 hour then 60–95°C for 2 hours afforded 3-formyl-9-(dimethylaminomethylene)pyridopyrimidin-4-ones **406** [83JCS(P1)369; 84JMC1253]. Formylation occurred first at position 9 and then the aminomethylene group activated position 3 for further reaction. This time the 2-methoxy derivative **405** ( $R = OMe$ ) also yielded the 2-chloro derivative **406** ( $R^2 = Cl$ ) [83JCS(P1)369]. While 9-[(*N*-methyl-*N*-phenylamino)meth-



ylene derivative **407** [ $R = N(\text{Me})\text{Ph}$ ] afforded 3-formyl derivative **408** on treatment of a mixture of phosphoryl chloride and dimethylformamide at room temperature for 1 hour, then  $100^\circ\text{C}$  for 1 hour, the 9-ethoxycarbonylmethylene compound **407** ( $R = \text{COOEt}$ ) was recovered unchanged.

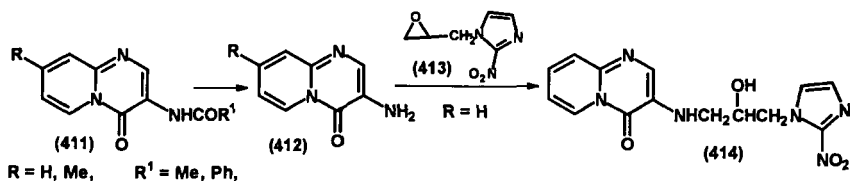


Reaction of 3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **409** with [(ethoxycarbonyl)methylene]triphenylphosphorane in a Wittig reaction in dimethylformamide at ambient temperature for 10 hours gave 3-*trans*-acrylates **410** (92JHC559). The 3-formyl group of 3,9-diformyl-1,6,7,8,9-tetrahydro and 3-formyl-9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines was transformed to a *trans*-acrylate side chain in a Wittig reaction with [(ethoxycarbonyl)methylene]triphenylphosphorane in dimethyl sulfoxide at room temperature for 24 hours (84JMC1253).



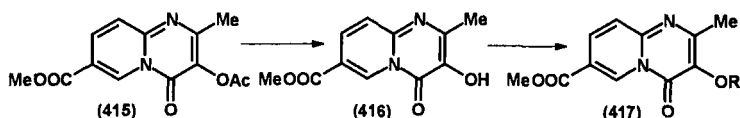
Hydrolysis of 3-benzamido-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **411** in 1 : 1 diluted or concentrated hydrochloric acid at reflux, or at  $65\text{--}75^\circ\text{C}$ , afforded 3-amino derivatives **412** in 80% and 28% yields, respectively (81GEP2932703; 85JHC481). The amino group of 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **412** ( $R = \text{H}$ ) reacted with 1-(2,3-epoxypropyl)-2-nitroimidazole **413** in boiling ethanol for 15 hours to give 3-alkylamino derivative **414** in 19% yield (92JMC1920).

The amino group of compound **412** ( $R = \text{Me}$ ) was reacted first with *N,O*-bis(trimethylsilyl)acetamide in boiling acetonitrile, then with *D*- $\alpha$ -amino(4-hydroxyphenyl)acetic acid in tetrahydrofuran or with phosgene in tetrahy-

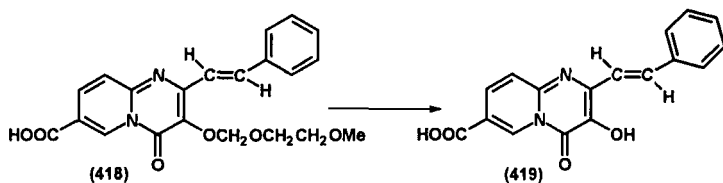


drofuran in the presence of triethylamine, and finally with amoxycillin trihydrate in 85% aqueous tetrahydrofuran in the presence of triethylamine at pH 8.2 at 0°C (81GEP2932703). The amino group of the phenylacetic acid moiety was involved in a further reaction.

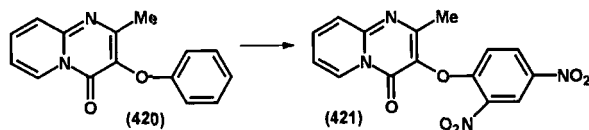
Treating 3-acetoxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate **415** with sodium hydrogen carbonate in methanol at 60°C for 4 hours, then at ambient temperature for 16 hours, gave 3-hydroxypyridopyrimidine-7-carboxylate **416** (84FES837). The free hydroxyl group of compound **416** was alkylated with an alkyl iodide in dimethylformamide in the presence of potassium carbonate at room temperature or with 2-methoxyethoxymethyl chloride in dichloromethane in the presence of diisopropylethylamine at ambient temperature for 3 hours to give 3-alkoxy derivatives **417**.



3-Hydroxy-2-(2-phenylvinyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylic acid **419** was prepared from 3-(2-methoxyethoxymethoxy) derivative **418** by treatment with 35% hydrochloric acid in methanol at 45°C (84FES837).



Nitration of 2-methyl-3-phenoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **420** with a 1:2 mixture of concentrated nitric and sulfuric acids at room temperature for 1 hour led to 3-(2,4-dinitrophenoxy) derivative **421** (83H1083).



Ester groups of different 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and 3-acrylates were easily hydrolyzed under acidic or basic conditions (82USP4321377; 83JMC1494, 83MIP1, 83URP999973; 84JMC1253, 84S582, 84USP4461769; 85ACH305; 87H869).

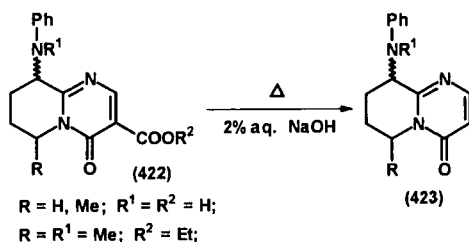
4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and its homologs were hydrolyzed to the appropriate carboxylic acids under acidic (a mixture of 6 *N* hydrochloric acid and acetic acid at 80°C) (87EUP242230) or basic conditions (a mixture of aqueous sodium hydroxide and ethanol or tetrahydrofuran) at 20–40°C (88USP4777252; 92AJC1825; 93MIP3). 9-Phenylamino-6,7-dihydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids were prepared from the ethyl esters in 4% aqueous sodium hydroxide at 60–70°C in good yields (85JHC1253).

4-Methoxybenzyl 9-(benzyloxycarbonyl)thio- and 9-(dimethylcarbamoyl)thio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates were hydrolyzed in dichloromethane by the action of trifluoroacetic acid in the presence of anisole at 0°C (87EUP218423).

2-Substituted 6-methyl-9-phenylhydrazono-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides were hydrolyzed by heating in boiling concentrated hydrochloric acid to give 2-substituted tetrahydropyridopyrimidine-3-carboxylic acids (83JMC1126).

9-Hydrazono-6-methyl-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid was esterified in ethanol in the presence of hydrogen chloride at 10–15°C overnight (83OMR687, 83URP999973; 84USP4461769).

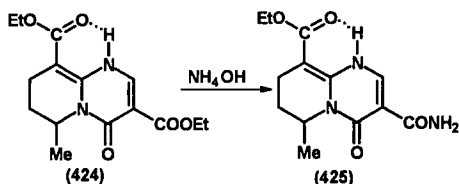
6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared by the decarboxylation of 6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid in 85% phosphoric acid at 160–170°C for 6 hours (85ACH305). Decarboxylation of 9-anilino-4-oxotetrahydropyridopyrimidine-3-carboxylic acid derivatives **422** occurred in refluxing 2% aqueous sodium hydroxide under argon to give 3-unsubstituted derivatives **423** [85JCS(P1)1015].



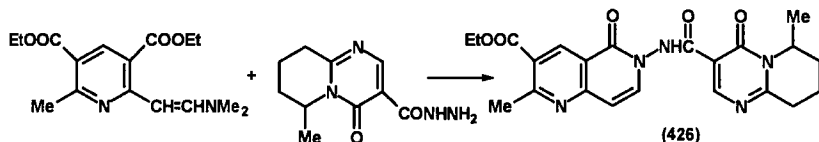
The ester groups of 4-oxo-4*H*-, 6,7,8,9-tetrahydro-4-oxo-4*H*-, and 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates reacted with ammonia and hydrazide to give 3-carboxamides and 3-carbohydrazides, respectively (82JMC1140, 82USP4321377; 83MIP1, 83SZP635100, 83URP999973; 84S582, 84USP4461769; 85JOC2918; 88EUP252809).

Reaction of diethyl 6-methyl-1,6,7,8-tetrahydro-4-oxo-4*H*-pyrido[1,2-

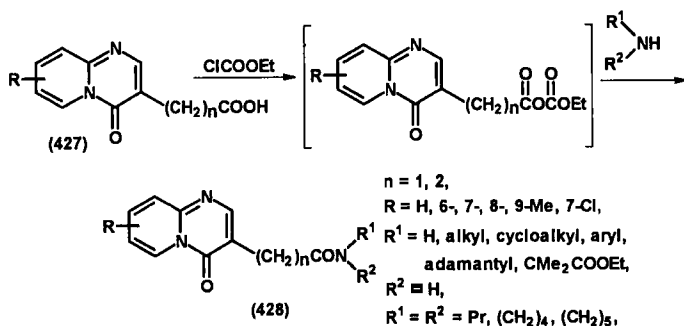
*a*]pyrimidine-3,9-dicarboxylate **424** with aqueous ammonia in ethanol at ambient temperature afforded ethyl 3-aminocarbonyl-6-methyl-1,6,7,8-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylate **425** (82USP-432177;83MIP1).



The amino moiety of the 3-carbohydrazide group of unsaturated and 6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbohydrazides was condensed with acetone and 5-nitro-2-furaldehyde (83OMR687; 88EUP252809). The reaction of 6-methyl-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbohydrazide with diethyl 2-[2-dimethyl-amino)vinyl]-6-methylpyridine-3,5-dicarboxylate in boiling ethanol for 4 hours afforded *N*-(1,6-naphthyridin-6-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide **426** (85MIP1).

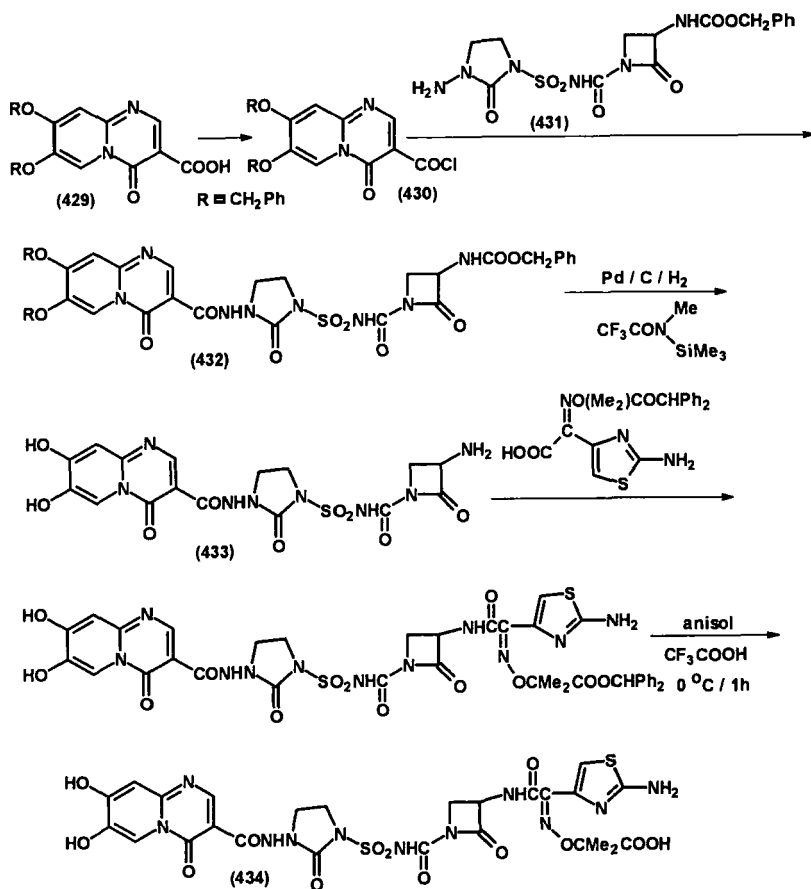


*N*-Substituted and *N,N*-disubstituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides and -3-acetamides **428** ( $n = 0, 1$ ) were prepared from the corresponding carboxylic acid **427** when the carboxylic acids were reacted first with methyl chloroformate in the presence of triethylamine in chloroform at  $-20^{\circ}\text{C}$ , after which the mixed anhydrides were treated with an amine at  $-10^{\circ}\text{C}$  overnight (89EUP326981).



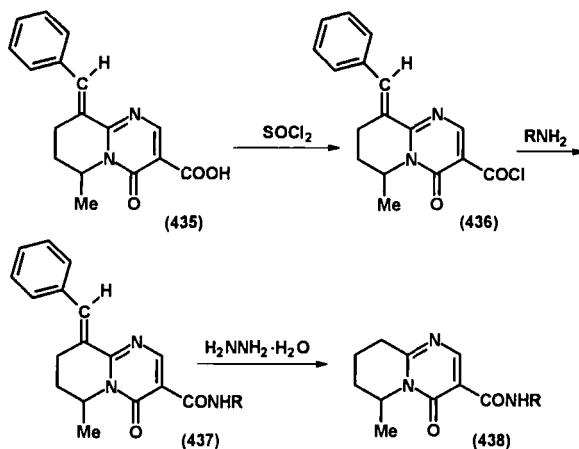
The treatment of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid **429** with phosphorus pentachloride in dichloromethane at 0°C gave acid chloride **430**, which reacted with amine **431** in tetrahydrofuran in the presence of *N*-methyl-*N*-trimethylsilyl trifluoroacetamide at room temperature overnight to give *N*-substituted 3-carboxamide **432** (88USP4777252). After catalytic debenzoylation, the 3-substituent of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **433** was involved in different reactions to give antibacterial derivative **434** (see Scheme 25).

9-Benzylidene-6-methyl-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid **435** was converted to 3-carbonyl chloride **436** on treatment with boiling thionyl chloride for 2 hours. Then the crude



SCHEME 25

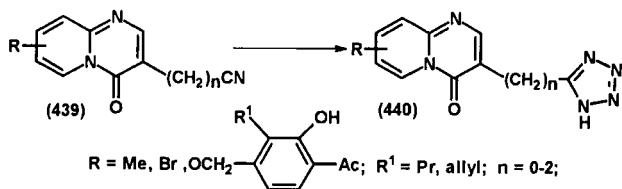
acid chloride **436** was reacted with primary amines in a boiling solvent in the absence or presence of a base for 4–5 hours to give 9-benzylidenetetrahydropyridopyrimidine-3-carboxamides **437**. The treatment of 9-benzylidenetetrahydropyridopyrimidine-3-carboxamides **437** with hydrazine hydrate in boiling ethanol yielded 9-unsubstituted tetrahydropyridopyrimidine-3-carboxamides **438** (84MIP2, 84S582). Tetrahydropyridopyrimidine-3-carboxamides **438** could not be prepared directly from 9-un-



substituted 6,7,8,9-tetrahydro-4-oxo-4*H*-pyridopyrimidine-3-carboxylate with an amine because they suffered ring transformation to 4-hydroxy-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylates on heating in the presence of an amine (79H1407). The 3-carbonyl chloride could not be prepared from 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids with thionyl chloride because an active methylene group was present at position 9. So the 9-benzylidene group played a role as a protective group of the active methylene group in the above reaction.

6,7,8,9-Tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile was prepared when 6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide was treated with phosphoryl chloride in the presence of a catalytic amount of polyphosphoric acid at 98–100°C for 1 hour (82JMC1140).

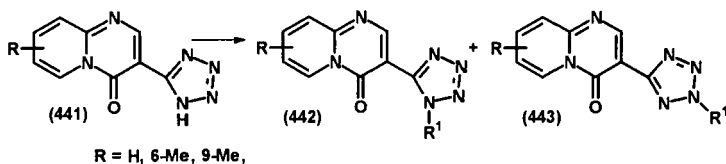
The cyano group of 3-cyano-, 3-cyanomethyl-, and 3-( $\omega$ -cyanoalkyl)-4*H*-pyrido[1,2-*a*]pyrimidinones **439** was converted to a 5-tetrazolyl group by treatment with sodium azide in boiling tetrahydrofuran for 2–23 hours in the presence of aluminum chloride or in dimethylformamide at 100–110°C for 8 hours in the presence of ammonium chloride to yield 5-tetrazolyl derivatives **440** [87EUP217673; 88JAP(K)88/246375]. 3-(1*H*-



Tetrazol-5-yl)-9-(dimethylcarbamoylthio)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained when the appropriate 3-nitrile was treated with a mixture of sodium azide and aluminum chloride in tetrahydrofuran (89EUP329126).

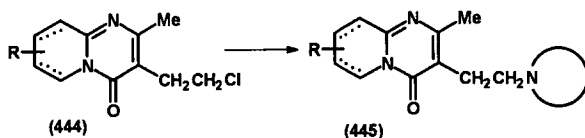
When 4-imino-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitrile reacted with sodium azide in a solvent at 60–70°C for 3–6 hours, ring-opened 3-[(3-methyl-2-pyridyl)amino]-2-(1-*H*-tetrazol-5-yl)-2-propenenitrile was obtained, but the bicyclic 4-imino-9-methyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidine could be isolated when the reaction was carried out in acetic acid at 115°C (90EUP385634). The latter product was also obtained from the ring-opened product by heating in 1*N* hydrochloric acid at 100°C for 1 hour, or in 1*N* potassium hydroxide at 100°C for 3.5 hours. Reaction in acetic acid was also extended to 9-phoxymethyl, 9-(4-acetyl-3-hydroxy-2-propylphenoxy)methyl, and 9-(4-isopropylphenoxy)methyl derivatives.

3-(5-Tetrazolyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **441** were alkylated with alkyl iodides, alkyl bromides, triethyl phosphate, cyclopentyl bromide, allyl bromide, propargyl bromide, benzyl chlorides, ethyl bromoacetate, and methyl chloroformate in dimethylformamide in the presence of potassium carbonate at 80–90°C to give a mixture of 3-(1-substituted 5-tetrazolyl)- and 3-(2-substituted 5-tetrazolyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **442** and **443**, which could be separated by fractional crystallization or by column chromatography (93MIP1).



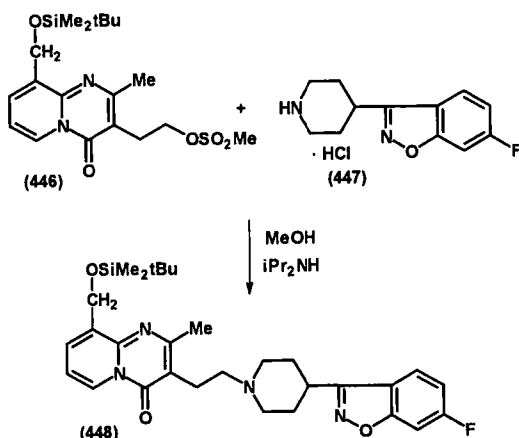
The chloro atom of the 3-(2-chloroethyl) moiety of unsaturated 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **444** reacted with different cyclic amines to yield 3-(2-aminoethyl) derivatives **445** [81EUP37265; 82USP4342870; 84EUP110435; 85EUP144101, 85EUP151826; 86EUP-196132, 86EUP206415; 87USP4695575; 88EUP282133; 89EUP297661, 89JAP(K)89/06269, 89JAP(K)89/31782; 90EUP353821, 90EUP357134,





90EUP368388, 90EUP372776, 90EUP393738, 90USP4957916; 91EUP-453042, 91MIP4; 92EUP518434, 92MIP1-92MIP3, 92USP5158952; 93EUP518435, 93MIP4, 93MIP5]. Usually, a catalytic amount of sodium or potassium iodide was added to the reaction mixtures. According to these procedures, pirenperone **5** ( $R = H$ ), seganserine **6**, risperidone **7**, ocaperidone **8**, and ramastine **9** were also prepared. Ocaperidone **8** and its 6,7,8,9-tetrahydro derivative were also prepared from 3-(2-bromoethyl)-2,9-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and from its 6,7,8,9-tetrahydro derivative with 1,2-benzisoxazole hydrochloride in methyl ethyl ketone in the presence of sodium carbonate and a catalytic amount of potassium iodide at room temperature overnight (91EUP453042).

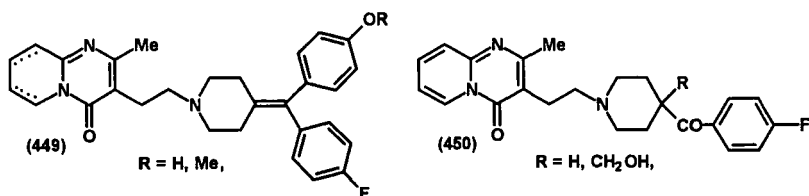
The hydroxy group of 3-(2-hydroxyethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **104** was mesylated by mesyl chloride in pyridine at 0°C, then the mesylated derivative **446** was reacted with 1,2-benzisoxazole hydrochloride **447** in methanol in the presence of diisopropylamine at 60°C for 68 hours to yield 3-(2-aminoethyl)pyridopyrimidin-4-one derivative **448** (91EUP453042).



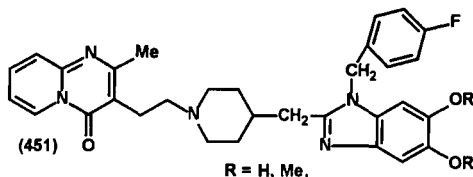
4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones **449** ( $R = H$ ) were alkylated with methyl iodide in the presence of sodium hydride in dimethylformamide to yield methoxy derivative **449** ( $R = Me$ ) (84EUP110435).

Reaction of pirenperone **5** ( $R = H$ ) with paraformaldehyde and 40% benzyltrimethylammonium hydroxide in methanol at 60–70°C in piperidine

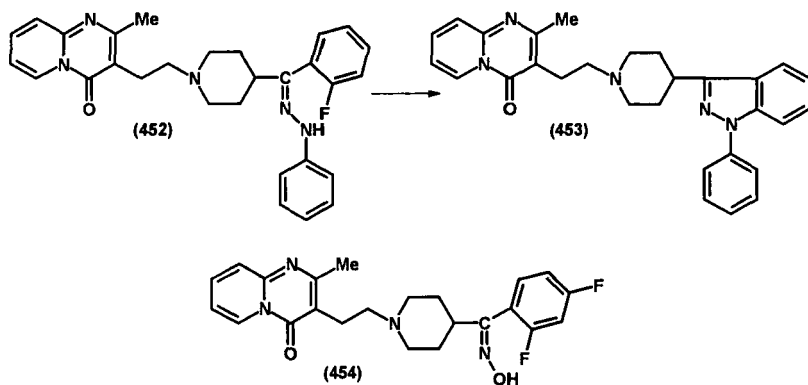
for a week gave hydroxymethyl derivative **450** ( $R = \text{CH}_2\text{OH}$ ) in 16% yield (81EUP37265; 82USP4342870).



The treatment of dimethoxy derivative **451** ( $R = \text{Me}$ ) with 48% aqueous hydrogen bromide at  $80^\circ\text{C}$  overnight yielded the trihydrobromide salt of dihydroxy derivative **451** ( $R = \text{H}$ ) (87USP4695575).

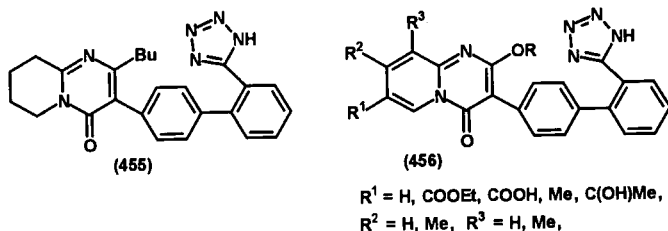


The cyclization of 3-[2-[4-[(2-fluorophenyl)-(2-phenylhydrazono)methyl]-1-piperazinyl]ethyl]-2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one **452** in boiling ethylene glycol in the presence of potassium carbonate overnight gave indazole derivative **453** in 25% yield (90EUP353821, 90USP4957916). Ocaperidone **8** was obtained when the *Z* oxime **454** was stirred in toluene in the presence of aqueous potassium hydroxide at  $45\text{--}55^\circ\text{C}$  for 0.5 hour, then at reflux for 3 hours (91EUP453042).

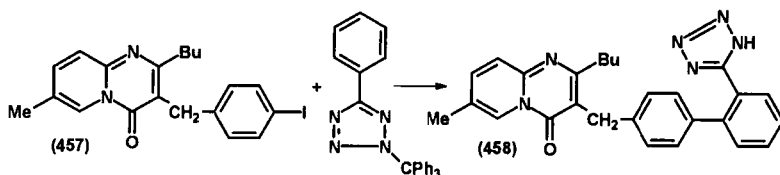


It was claimed that tetrazolyl derivative **455** was prepared from the appropriate nitrile on treatment with tributyltin azide in boiling *o*-xylene

(91EUP435827). Tetrazolyl derivatives **456** were obtained from the corresponding nitrile on treatment with sodium azide and tributyltin chloride in refluxing xylene (94MI2).



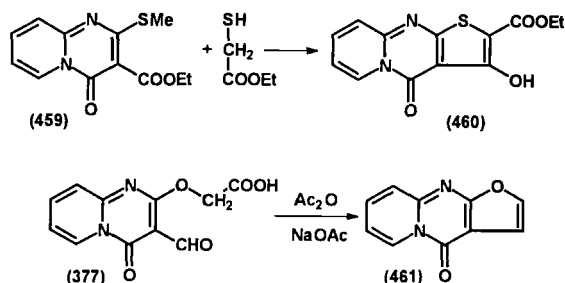
Unsubstituted tetrazolyl derivative **458** was also prepared according to the following procedure (91MIP2). A solution of 5-phenyl-2-trityltetrazole in tetrahydrofuran was first treated with 1.7 *M* *tert*-butyllithium in pentane at  $-25^\circ\text{C}$ , in two parts. After about 30 minutes, an organolithium salt precipitated. Then a 1 *M* ethereal solution of zinc chloride was added to the mixture, which was then warmed to room temperature. Bis(triphenylphosphine)palladium(II) chloride and 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **457** were added to the reaction mixture, and after boiling for 4 hours, the 2-trityl derivative of **458** was obtained in 56% yield. Finally, detritylation with a mixture of methanol and concentrated hydrochloric acid yielded tetrazole derivative **458**.



## 6. Cyclizations Involving Positions 2 and 3 of Pyrido[1,2-*a*]pyrimidin-4-ones

Cyclocondensation of ethyl 2-methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **459** and ethyl mercaptoacetate in acetonitrile in the presence of potassium carbonate at  $60^\circ\text{C}$  for 2 hours, then at room temperature for 16 hours gave pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-2-carboxylate **460** (88CP1232904).

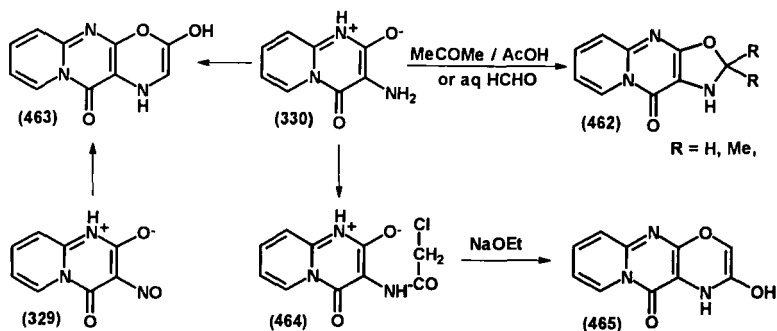
2-[(Carboxy)methoxy]-3-formylpyrido[1,2-*a*]pyrimidin-4-one **377** was cyclized by heating in acetic anhydride to give furo[2,3-*d*]pyrimidinone **461** [91IJ(C)839].



The reaction of 3-aminopyridopyrimidin-4-one **330** with acetone in boiling dichloromethane in the presence of a catalytic amount of acetic acid for 5 hours followed by 24-hour stirring at room temperature or with 37% aqueous formalin in boiling ethanol for 2 hours afforded tricyclic oxazolo[5,4-*d*]pyrido[1,2-*a*]pyrimidinones **462** [91IJC(B)839].

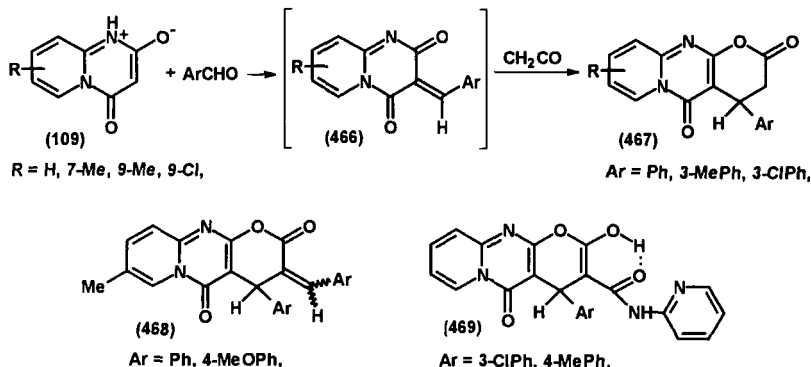
It was suggested that tricyclic oxazino[6,5-*e*]pyrido[1,2-*a*]pyrimidinone **463** was obtained both in the reaction of 3-aminopyridopyrimidinone **330** and 3-nitrosopyridopyrimidinone **329** with ethyl bromoacetate in boiling ethanol in the presence of sodium ethylate for 4 hours [91IJC(B)839]. When 3-aminopyridopyrimidinone **330** was first acylated with chloroacetyl chloride in refluxing benzene and the resulting acetamido derivative **464** heated in boiling ethanol in the presence of sodium ethylate, isomeric hydroxyl derivative **465** was obtained (Scheme 26) [91IJC(B)839].

Reactions of malonyl- $\alpha$ -aminopyridines **109** with excess aromatic aldehydes at reflux for 10–30 minutes afforded tricyclic pyridopyranopyrimidines **467** (90ZC98). In the first step of the reaction condensation product **466** was formed, which reacted with ketene in a (4+2)-cycloaddition to yield tricyclic compounds **467**. Ketene was formed by decomposition of another molecule of malonyl- $\alpha$ -aminopyridine **109** together with the

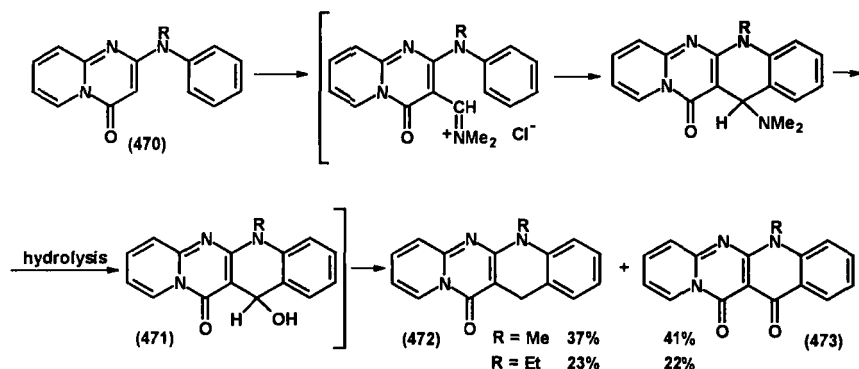


SCHEME 26

formation of 2-pyridyl isocyanates. Sometimes other products (**468** and **469**) were also isolated from the reaction mixtures in accordance with the proposed mechanism.

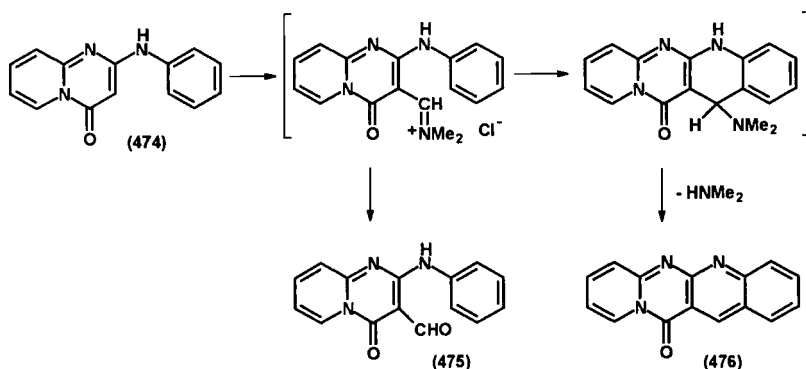


Vielsmeier–Haack formylation of *N*-substituted 2-phenylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **470** with a mixture of phosphoryl chloride and dimethylformamide at 95°C for 90 minutes gave a near 1:1 mixture of pyrido[1',2':1,2]pyrimido[4,5-*b*]quinazolin-12-one **472** and -12,13 dione **473** in 23–37% and 22–41% yields, respectively (87JHC329). Compounds **472** and **473** probably formed by the disproportionation of the tetracyclic hydroxyl derivatives **471**. If the substituent (R) of **470** was the ethoxycarbonyl group, only *N*-ethoxycarbonyl derivative **475** could be obtained (92JHC25). No tetracyclic derivative **472** and/or **473** (R = COOEt) was formed.

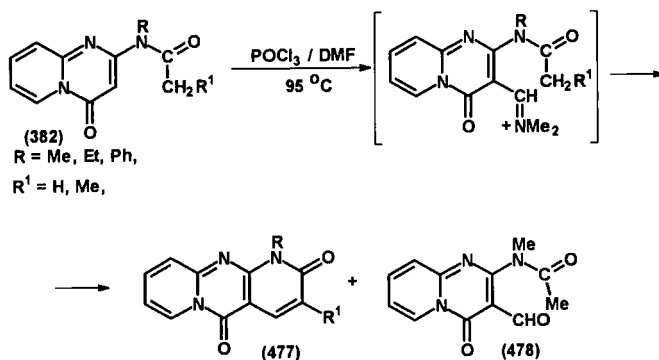


When 2-phenylamino derivative **474** reacted under the above conditions, unsaturated 12*H*-pyrido[1',2':1,2]pyrimido[4,5-*b*]quinolin-12-one **476** and 3-formyl-2-phenylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **475** were isolated in 57% and 11% yields, respectively. When the reaction was carried

out at 45°C, tetracyclic product **476** was obtained in just 8.1% yield, and 3-formyl derivative **475** in 77% yield (87JHC329).



2*H*-Dipyrido[1,2-*a*:2',3'-*d*]pyrimidine-2,5(1*H*)-diones **477** were prepared when 2-acylamido-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **382** were heated in a mixture of phosphoryl chloride and dimethylformamide (92JHC25). When the reaction period was only 15 minutes, 2-acetamido derivative **382** (R = Me, R<sup>1</sup> = H) gave 3-formyl derivative **478** and tricyclic compound **477** (R = Me, R<sup>1</sup> = H) in 31% and 53% yields, respectively.

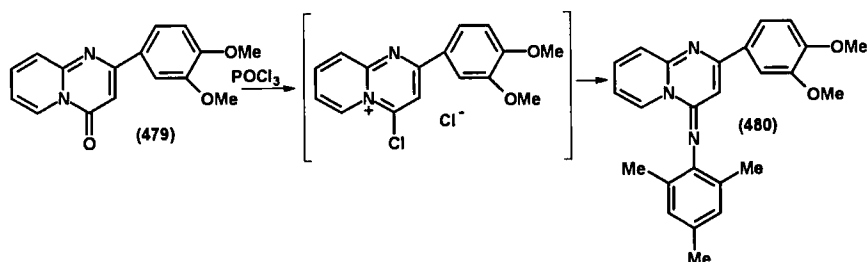


## 7. Reactions Involving Position 4 of the Pyrido[1,2-*a*]pyrimidine Ring and Cyclizations Involving Positions 4 and 6

7-, 8-, and 9-Substituted 3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were prepared when 9-substituted 4-imino-3-[1*H*-tetrazol-5-yl]-4*H*-pyrido[1,2-*a*]pyrimidines were heated in 1 *N* hydrochloric acid at

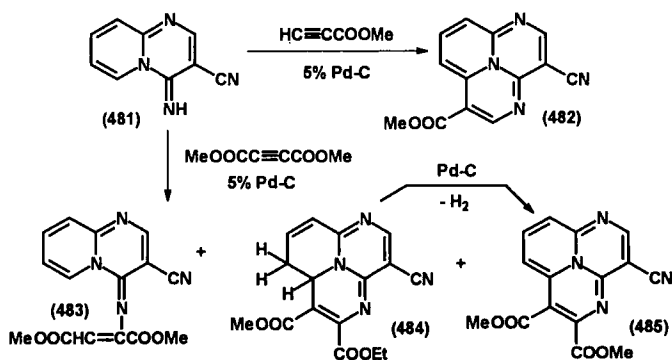
80°C for 3.5 hours, or when 9-substituted 3-cyano-4-imino-4*H*-pyrido[1,2-*a*]pyrimidines were reacted with sodium azide in aqueous hydrochloric acid at room temperature for 3 hours followed by heating at 90°C for 1 hour, or with azide in acetic acid at 115°C for 1 hour followed by the addition of concentrated hydrochloric acid and heating at 100°C for 2 hours (90EUP385634).

When 2-(3,4-Dimethoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **479** was boiled in phosphoryl chloride for 1 hour, the reaction mixture was evaporated and the residue was treated with 2,4,6-trimethylaniline at 100–120°C for 1 hour, 4-arylamino derivative **480** was obtained (86EUP168262).



Cycloaddition of methyl propiolate to 4-imino-4*H*-pyrido[1,2-*a*]pyrimidin-4-imine **481** in the presence of 5% palladium-on-charcoal catalyst as dehydrogenating agent yielded cyclazine derivative **482** in 12% yield (Scheme 27) (87YZ344). A similar reaction with dimethyl acetylenedicarboxylate gave a mixture of addition (**483**), cycloaddition (**484**), and dehydrogenated (**485**) products in 16%, 23%, and 37% yields, respectively.

3-Ethyl-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-thione was obtained in



SCHEME 27

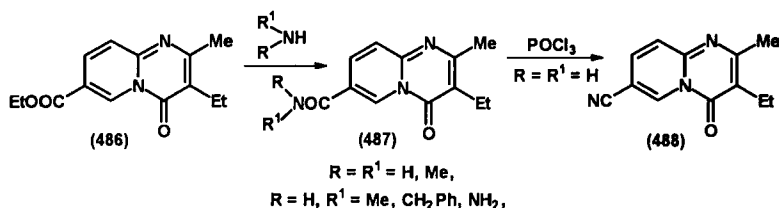
the reaction of the pyridopyrimidin-4-one **347** with phosphorus pentasulfide. The 4-thione group was alkylated with methyl iodide to yield 4-(methylthio)pyrido[1,2-*a*]pyrimidinium iodide (82MI6). Other 4*H*-pyrido-pyrimidin-4-thiones were also prepared similarly (93MI8).

#### 8. Reactions Involving the 7- and 8-Substituents of Pyrido[1,2-*a*]pyrimidines and Cyclization Involving Positions 6 and 7 or Positions 8 and 9

The 7- and 9-carboxyl group of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was esterified by heating in ethanol in the presence of hydrogen chloride (83PHA218) or in dimethylformamide with methyl iodide in the presence of potassium carbonate at ambient temperature (83MI12).

The ester group of methyl 3-alkoxy-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate was hydrolyzed to a carboxyl group when the 2-methyl group reacted with benzaldehyde in the presence of sodium methoxide in boiling methanol for 20 hours (84FES837).

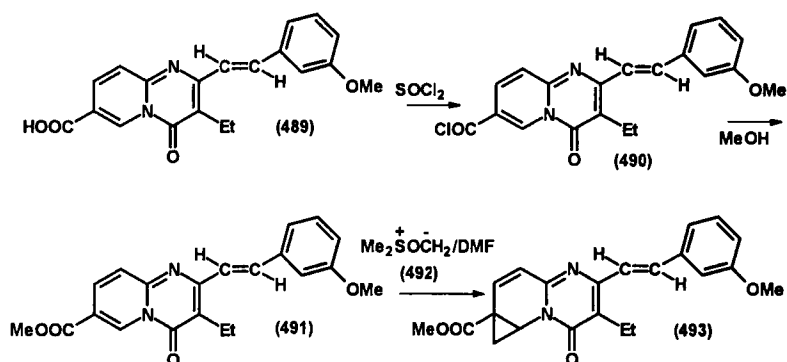
Ethyl 3-ethyl-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate **486** reacted with ammonia, methylamine, and dimethylamine in methanol at ambient temperature for 3 days, with benzylamine at 175°C for 1 hour, and with hydrazine in boiling ethanol for 1 hour to afford the appropriate 7-carboxamides **487** and 7-carbohydrazide (83PHA218). The treatment of 7-carboxamide **487** ( $R = R^1 = H$ ) with boiling phosphoryl chloride for 1 hour afforded 7-nitrile **488**. 7-Carboxylic acid chloride **490** was



prepared from 7-carboxylic acid **489** with thionyl chloride in refluxing dioxane for 2 hours (83MI12). The acid chloride **490** was treated with methanol in the presence of pyridine at reflux for 2 hours to give the methyl ester **491**. The methyl ester **491** was reacted with ylide **492**, prepared from trimethylsulfonium iodide with 50% sodium hydride in dimethylformamide, at room temperature for 1 hour to give 6,7-methylene-4-oxo-4*H* pyrido[1,2-*a*]pyrimidine-7-carboxylate **493**. Similarly, 3-propyl-2-{*trans*-[2-(2'-methylphenyl)ethenyl]} derivative of **493** was also prepared.

Ethyl 3-(7-bromomethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)propionate reacted with 2,4-dihydroxy-3-propylacetophenone in boiling methyl



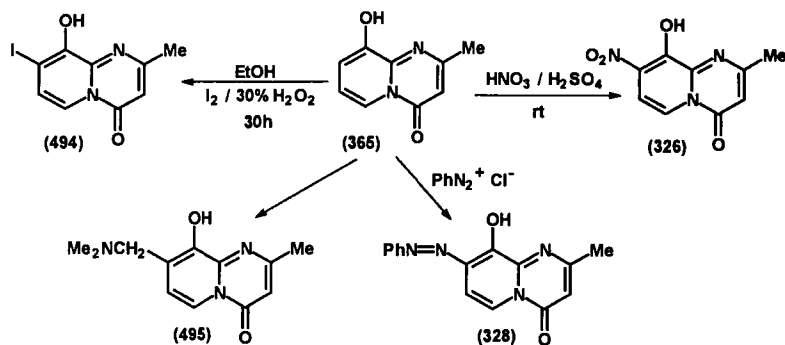


ethyl ketone for 2 hours to yield ethyl 3-[7-(4-acetyl-3-hydroxy-2-propyl-phenoxy)methyl]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]propionate (87-EUP242230).

The ester group of 3-ethyl-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-8-carboxylate reacted with 15% ammoniacal methanol at ambient temperature overnight to give an 8-carboxamide derivative (83PHA218).

3,8-Dinitro-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained when 3-nitro-9-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was treated with a mixture of concentrated sulfuric and concentrated nitric acids at 0°C for 1 hour [90JCR(S)308].

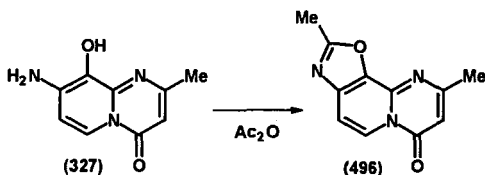
9-Hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **365** gave 8-substituted derivatives in a reaction with different electrophilic reagents (Scheme 28) (92KGS1660). Nitration gave 8-nitro-9-hydroxy-2-methylpyridopyrimidin-4-one **326**. Reaction with iodine afforded 8-iodo-9-hydroxy derivative **494** in 28% yield. Reaction with *N,N,N,N*-tetramethylmethylenediamine gave 8-(dimethylamino)methyl-9-hydroxy



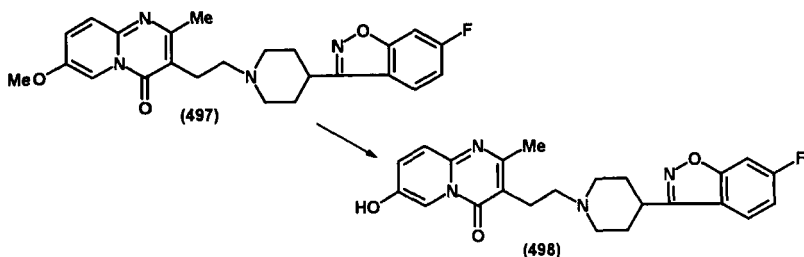
SCHEME 28

derivative **495**. 8-Phenylazo-9-hydroxy-2-methyl-4*H*-pyridopyrimidin-4-one **328** was obtained when 9-hydroxy-2-methyl derivative **365** reacted with phenyldiazonium chloride (see also Section IV,C,5).

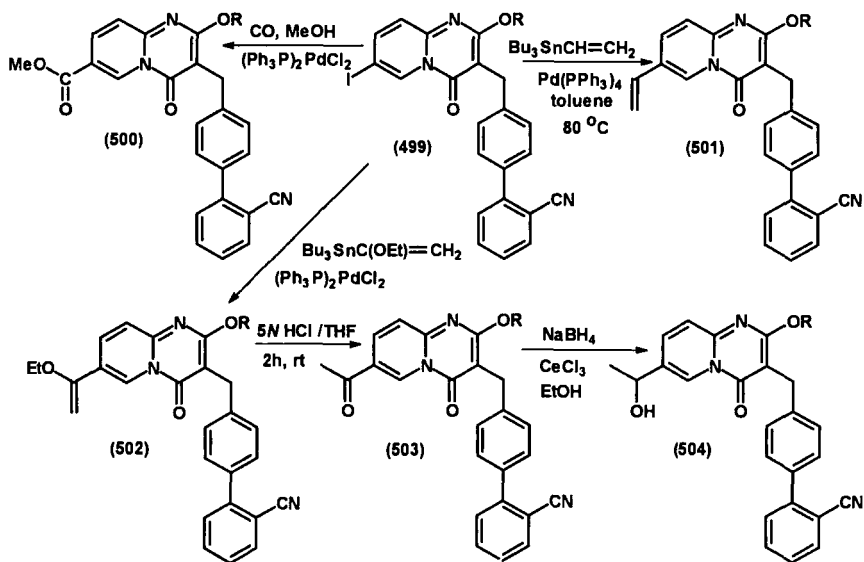
7*H*-Oxazolo[5,4;3,4]pyrido[1,2-*a*]pyrimidin-4-one **496** was prepared in the reaction of 8-amino-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **327** and acetic anhydride for 24 hours (92KGS1660).



The treatment of 7-methoxy-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **497** with iodotrimethylsilane in acetonitrile at 70°C overnight, and then with another portion of iodotrimethylsilane at 90°C followed by heating at reflux overnight, gave a 3.7% yield of 7-hydroxy-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **498** after work-up (90EUP368388; 92USP5158952). The 7-hydroxyl group of **498** was acylated with decanoyl chloride in a mixture of methylene chloride and water at room temperature in the presence of sodium hydroxide.



4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylates **500** were obtained when 7-iodo-4*H*-pyrido[1,2-*a*]pyrimidines **499** reacted with carbon monoxide in the presence of bis(triphenylphosphine)palladium(II) chloride catalyst and triethylamine (Scheme 29) (94MI2). From 7-iodo derivatives **499**, 7-vinyl derivatives **501** and 7-(1-ethoxyvinyl) derivatives **502** were prepared with vinyltributyltin in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> and with (1-ethoxyvinyl)tributyltin in the presence of bis(triphenylphosphine)palladium(II) chloride catalyst, respectively, in toluene at 80°C. 7-(1-Ethoxyvinyl)pyrido[1,2-*a*]pyrimidin-4-ones **502** were hydrolyzed to yield 7-acetyl derivatives **503**. The acetyl group of compounds **503** was reduced with sodium borohydride in the presence of cerium(III) chloride in ethanol to give 7-(1-hydroxyethyl)pyridopyrimidin-4-ones **504**.



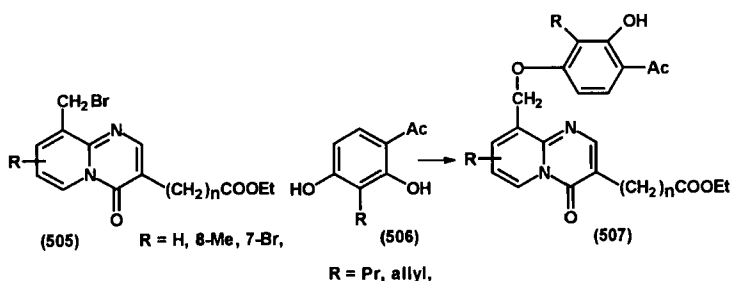
SCHEME 29

The 7,8-dibenzyloxy groups of *N*-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-carboxamide **333** were catalytically debenzylated under hydrogen over palladium-on-charcoal in dimethylformamide in the presence of *N*-methyl-*N*-trimethylsilyl trifluoroacetamide for 1 hour (88USP4777252).

### 9. Reactions Involving Position 9 or the 9-Substituent of Pyrido[1,2-*a*]pyrimidin-4-ones

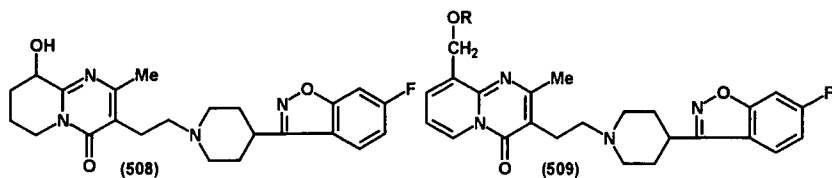
Reaction of 9-bromomethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **505** and their homologs with 2,4-dihydroxy-3-propyl- and -3-allyl-acetophenone **506** in boiling methyl ethyl ketone in the presence of potassium carbonate afforded 9-(4-acetyl-3-hydroxy-2-substituted phoxymethyl) derivatives (**507**) [87EUP242230; 88JAP(K)88/246375].

Besides the saturation of the double bonds of the pyridine ring, the 9-benzyloxy group was cleaved when 3-(2-chloroethyl)-2-methyl-9-benzyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **102** ( $\text{R} = 9\text{-OCH}_2\text{Ph}$ ) was hydrogenated over 10% palladium-on-charcoal catalyst in methanol at ambient temperature and normal pressure to give 9-hydroxy-6,7,8,9-tetrahydro derivative **338** (90EUP368388; 92USP5158952). The 9-hydroxyl group of racemic 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **508** was acylated with (+)-3,4-dihydro-1*H*-2-benzopyrane-2-carbonyl chloride in dichlorometh-

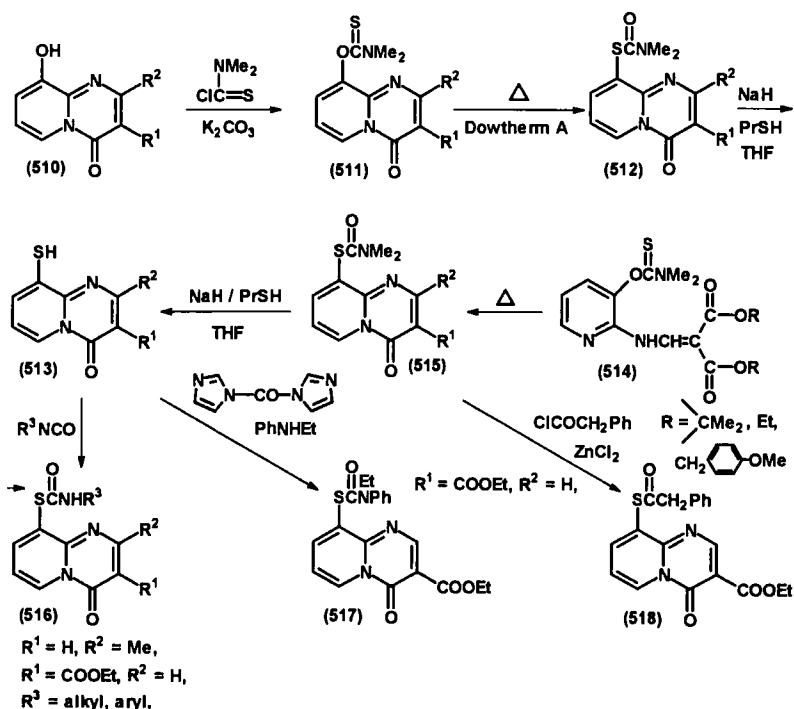


ane in the presence of 4-dimethylaminopyridine. The diastereomeric esters were separated by column chromatography, and after hydrolysis of the ester moiety, the optically active 9-hydroxytetrahydropyridopyrimidin-4-ones **508** were obtained in 3.6% yield. The 9-hydroxyl group of 4H-pyrido[1,2-*a*]pyrimidin-4-one **508** was also acylated with excess acetic anhydride at 50°C for 4 hours, and with decanoyl chloride in dichloromethane in the presence of aqueous sodium hydroxide at ambient temperature for approximately 20 hours.

The treatment of 9-silylated derivative **448** in tetrahydrofuran with tetrabutylammonium fluoride at ambient temperature for 45 minutes afforded 9-hydroxymethylpyrido[1,2-*a*]pyrimidin-4-one **509** ( $R = H$ ) in 54% yield (91EUP453042). After 9-hydroxymethyl derivative **509** ( $R = H$ ) reacted with decanoic acid in the presence of *N,N'*-methanetetraylbis(cyclohexanamine) and 4-(1-pyrrolidinyl)piperidine in dichloromethane under nitrogen at reflux for 4 hours with water removal, the reaction mixture was left to stand at ambient temperature for 24 hours to give 9-decanoyloxymethyl derivative **509** ( $R = \text{decanoyl}$ ).



9-Hydroxy-2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-ones **510** ( $R^1 = H$  or  $CN$ ;  $R^2 = H, Me$ ) reacted with dimethylthiocarbamoyl chloride in acetone to afford 9-dimethylthiocarbamoyloxy derivatives **511** ( $R^1 = H, CN$ ;  $R^2 = H, Me$ ) (Scheme 30) (87EUP218423; 89EUP329126). When compounds **511** were heated in Dowtherm A, the 9-dimethylthiocarbamoyloxy group rearranged to give 9-(dimethylcarbamoylthio)-2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-ones **512** in excellent yield. The treatment of pyridopyrimidin-4-one **512** ( $R^1 = H$ ,  $R^2 = Me$ ) with sodium hydride



SCHEME 30

(60% oil dispersion) and propyl mercaptan at room temperature for 24 hours gave 9-mercapto-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **513** ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Me}$ ) (87EUP218423).

Cyclization of 2-pyridylaminomethylenemalonates **514** in boiling Dowtherm A was accompanied by the rearrangement of the *N,N*-dimethylthiocarbamoyloxy group to give 9-*N,N*-dimethylcarbamoylthio-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **515** ( $\text{R}^1 = \text{H}$ , COOEt, COOCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>—4-OMe), which were converted to 9-mercaptopyridopyrimidines **513** ( $\text{R}^1 = \text{H}$ , COOCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>—4-OMe;  $\text{R}^2 = \text{H}$ ) on treatment with a mixture of sodium hydride and propyl mercaptan (87EUP218423).

The mercapto group of 9-mercapto-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **513** was alkylated with (het)aralkyl bromides and chlorides in the presence of potassium carbonate in dimethylformamide at ambient temperature for several hours. It also was acylated with carboxyl chlorides in the presence of potassium carbonate in acetone at room temperature or with mixed anhydride, prepared from aryl carboxylic acid and ethyl chloroformate,

in dimethylformamide at room temperature to yield 9-thioethers and thioesters, respectively (87EUP218423).

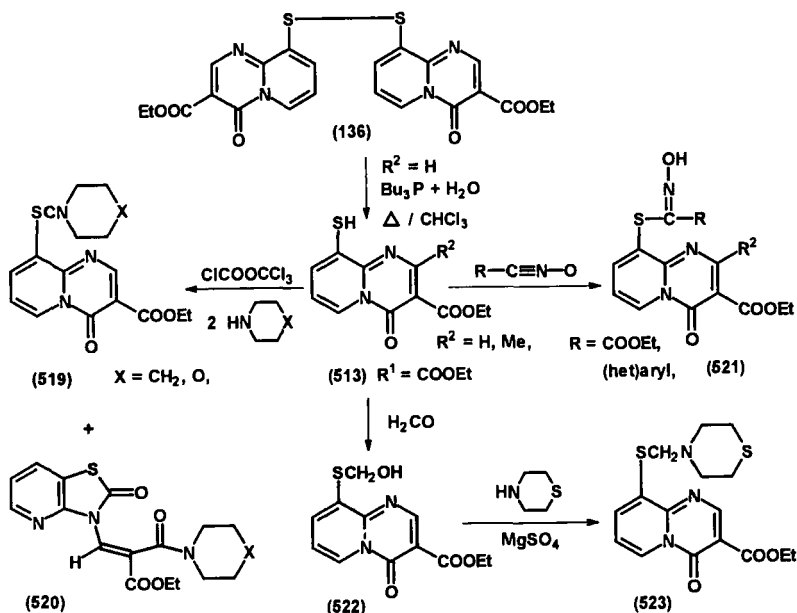
9-Mercapto-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **513** reacted with isocyanates in dichloromethane at ambient temperature to afford 9-(*N*-substituted carbamoylthio) derivatives **516** (87EUP218423).

Ethyl 9-mercapto-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **513** ( $R^1 = \text{COOEt}$ ,  $R^2 = \text{H}$ ) was also prepared from disulfide **136** in 54% yield (Scheme 31) (89EUP329126).

Ethyl 9-(*N*-ethyl-*N*-phenylcarbamoylthio)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **517** was obtained when 9-mercaptopyridopyrimidine-3-carboxylate **513** ( $R^1 = \text{COOEt}$ ,  $R^2 = \text{H}$ ) was first reacted with *N,N'*-carbonyldiimidazole in dichloromethane for 1 hour, and then the reaction mixture was treated with *N*-ethylaniline for another 16 hours (87EUP218423).

Reaction of ethyl 9-(dimethylaminocarbamoylthio)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxylate **515** ( $R^1 = \text{COOEt}$ ,  $R^2 = \text{H}$ ) with phenacetyl chloride in the presence of zinc chloride in refluxing 1,2-dichloroethane under nitrogen gave 9-(benzylcarbonyl)thio derivative **518** in good yield (87EUP218423).

The mercapto group of 9-mercapto-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-



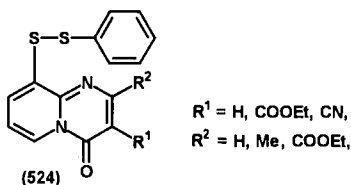
SCHEME 31

3-carboxylate **513** ( $R^1 = \text{COOEt}$ ,  $R^2 = \text{H}$ ) was treated with trichloromethyl chloroformate in dichloromethane at room temperature for 10 minutes; then the reaction mixture was concentrated at room temperature and the residue was dissolved in dichloromethane and reacted with a cyclic amine in the presence or absence of a base at ambient temperature to give a mixture of 9-(disubstituted carbamoylthio)pyridopyrimidine-3-carboxylate **519** and a ring-opened product **520** (Scheme 31) (89EUP329126). This type of 9-(disubstituted carbamoylthio) derivative (**519**) was also obtained when a cyclic amine was first reacted with trichloromethyl chloroformate in tetrahydrofuran, and then 9-mercaptopyridopyrimidin-4-one **513** ( $R^1 = R^2 = \text{H}$ ;  $R^1 = \text{COOEt}$ ,  $R^2 = \text{H}$ ) and triethylamine were added to the reaction mixture.

The reaction of 9-mercapto-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **513** ( $R^1 = \text{COOEt}$ ) and nitrile oxides in methylene chloride in the presence of trimethylamine at  $-20^\circ\text{C}$ , then at ambient temperature for 24 hours, afforded 9-substituted pyrido[1,2-*a*]pyrimidine-3-carboxylates **521** (89EUP329126).

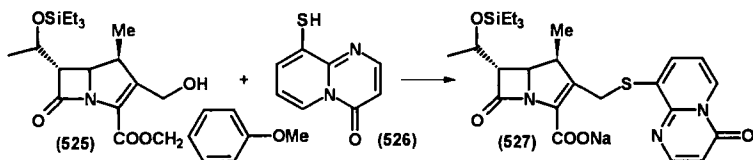
9-(Hydroxymethylthio)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **522**, prepared from 9-mercaptopyridopyrimidine-3-carboxylate **513** ( $R^1 = \text{COOEt}$ ,  $R^2 = \text{H}$ ) and 27% formaldehyde at  $100^\circ\text{C}$ , was reacted with thiomorpholine in the presence of magnesium sulfate in tetrahydrofuran under ice-cooling for 1 hour to afford 9-(4-thiomorpholinomethylthio)-pyridopyrimidine-3-carboxylate **523** (89EUP329126).

Reaction of 9-(dimethylcarbamoylthio)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **512** ( $R^1 = \text{H}$ ,  $\text{COOEt}$ ,  $\text{CN}$ ;  $R^2 = \text{H}$ ,  $\text{Me}$ ,  $\text{COOEt}$ ) with 2-nitrophenylsulfenyl chloride in the presence of zinc chloride in 1,2-dichloroethane at room temperature for 30–60 minutes afforded 9-(2-nitrophenyldithio)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **524** (89EUP329126).



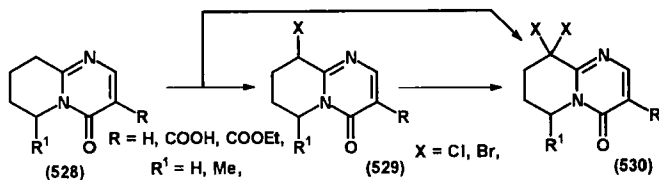
Treatment of the reaction mixture of carbapen-2-em-3-carboxylate **525**, triphenylphosphine, and 9-mercapto-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **526** in tetrahydrofuran with diethyl azodicarboxylate at room temperature for 1 hour gave sodium 2-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)thiomethyl-carbapen-2-em-3-carboxylate **527** after deprotection (91CPB663).

6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones contain an active methylene group at position 9. The reactivity of this group was lower than



that of the isomeric 6,7,8,9-tetrahydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones, but it was higher than that of the lower and higher homologs in the piperidine ring (82JHC909, 82MI4). The presence of a methyl group at position 6 and an electron-withdrawing group at position 3 increases the reactivity of the active methylene group, while an electron-donating methyl group at position 2 and/or 3 decreases it. The active methylene group easily reacted with different electrophilic reagents. Some reactions of the 9-methylene group and 9-substituent of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were earlier reviewed (91MI1–91MI3).

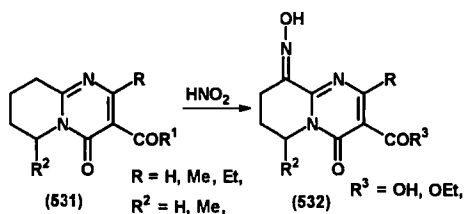
Depending upon the reaction circumstances and the molar ratio, 9-halogeno or 9,9-dihalogeno derivatives **529** and **530** could be prepared from 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **528**. Bromo derivatives were prepared with bromine in acetic acid in the presence of sodium acetate or with NBS in acetic acid, chloroform, or carbon tetrachloride; chloro derivatives were obtained with NCS in chloroform or acetic acid [83JCS(P2)1413; 85JHC1253; 87H869, 87JHC393; 91JHC1405]. The 9-monohalogeno-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **529** could be converted into the 9,9-disubstituted derivatives **530** under the above conditions.



The reaction of 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with excess bromine in acetic acid in the presence of sodium acetate afforded 3,9,9-tribromo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in good yield (83OMR687).

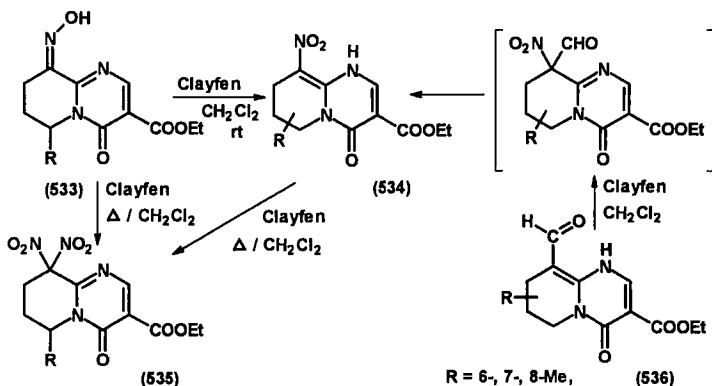
9-Hydroxyimino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **532** were obtained when 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **531** reacted with sodium nitrite in aqueous hydrochloric acid at 0°C or in aqueous sulfuric acid first at 60°C, then at 80°C (if  $R^1 = \text{NH}_2$ ) (83JMC1494). The hydroxy group of 9-hydroxyimino-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **533** ( $R = \text{Me}$ )





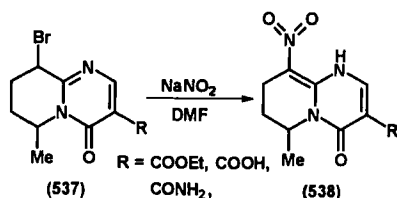
was ethylated on treatment with ethyl iodide in the presence of potassium carbonate in refluxing ethanol for 1 hour (83JMC1494).

When 9-hydroxyiminotetrahydropyridopyrimidine-3-carboxylates **533** ( $R = \text{H, Me}$ ) reacted with Clayfen [clay-supported iron(III) nitrate] at ambient temperature for 6 hours, 9-nitro-4-oxo-1,6,7,8-tetrahydro[1,2-*a*]pyrimidine-3-carboxylates **534** ( $R = \text{H, 6-Me}$ ) were obtained in 34–35% yields after column chromatography (Scheme 32) (90JOC6198). When the reaction mixtures were refluxed for 6–10 hours, 9,9-dinitro-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **535** ( $R = \text{H, 6-Me}$ ) were isolated in 25–31% yields. Dinitro compounds **535** were also prepared from 9-nitro derivatives **534** ( $R = \text{H, 6-Me}$ ) with Clayfen in 68–71% yields. When  $^{15}\text{N}$ -labeled 9-hydroxyimino compound **533** ( $R = \text{Me}$ ) was used, the  $^{15}\text{N}$  isotope remained in the 9-nitro group, indicating that oxidation of the oxime group to the nitro group occurred first, then nitration happened at the  $\beta$  position of the enamine moiety of 9-nitro-4-oxo-1,6,7,8-tetrahydropyridopyrimidine-3-carboxylate to give 9,9-dinitro derivative **535** ( $R = \text{Me}$ ). 9-Unsubstituted 6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (e.g., **531**:  $R = \text{H, } R^1 = \text{OEt; } R^2 = \text{H, Me}$ ) did not react with Clayfen in dichloromethane.

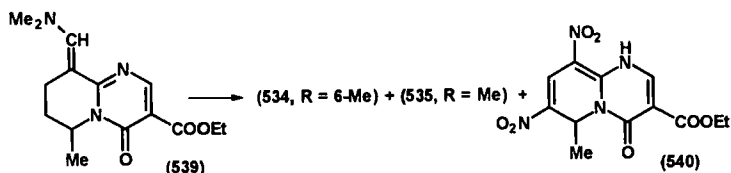


SCHEME 32

9-Nitro-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines **534** (*R* = 6-, 7-, and 8-Me) or **538** were also obtained from 9-formyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **536** with Clayfen in 24–54% yields (90JOC6198), or from 9-bromo-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **537** with sodium nitrite in 40–62% yields (87H869). From the reaction mixture of 9-formyl-6-methyltetrahydropyridopyrimidine-3-carboxylate **536** (*R* = 6-Me) both 32% of 9-nitro derivative **534** (*R* = 6-Me) and 5% of dinitro compound **535** (*R* = Me) were isolated following column chromatography (90JOC6198).



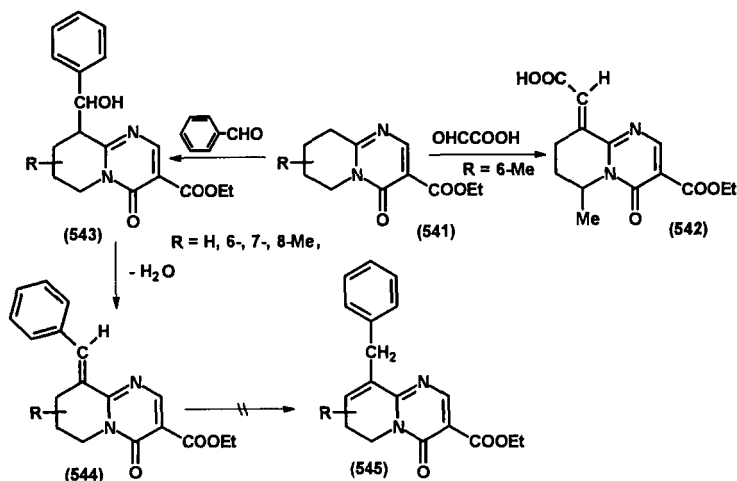
Reaction of ethyl 9-(dimethylaminomethylene)-4-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidine-3-carboxylate **539** with Clayfen in refluxing dichloromethane for 2.5 hours afforded a mixture of 9-nitro-1,6,7,8-tetrahydro (**534**; *R* = 6-Me), 9,9-dinitro-6,7,8,9-tetrahydro (**535**; *R* = Me), and ethyl 7,9-dinitro-1,6-dihydro-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **540** in 50%, 12%, and 12% yields, respectively (90JOC6198).



The active 9-methylene group of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones reacted with aldehydes to afford addition and/or condensation products (82MIP1; 84MIP2, 84S582; 89JHC1061; 91EUP453042).

Reaction of glyoxylic acid and tetrahydropyrido[1,2-*a*]pyrimidine-3-carboxylate **541** (*R* = 6-Me) in water at 70–75°C for 1 hour gave condensation product **542** with the *E* configuration (Scheme 33) (82MIP1).

When tetrahydropyridopyrimidinecarboxylates **541** were reacted with benzaldehyde in a melt below 40°C for 30 minutes, after which the reaction mixtures were diluted with ethanol and allowed to stand in a refrigerator at 0–5°C for a month, addition products **543** were obtained in about 20% yields (89JHC1061). If the reactions were carried out in boiling benzene in the presence of a few drops of concentrated hydrochloric acid for 5

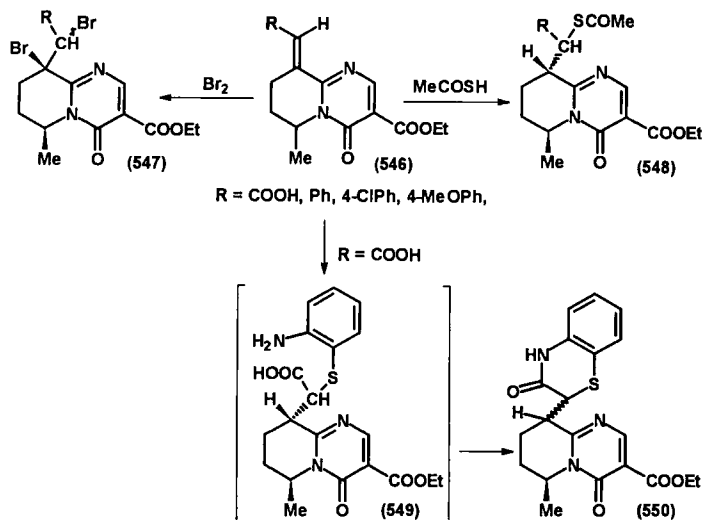


SCHEME 33

hours, condensation products **544** with the *E* configuration were obtained in 80% yields (84MIP2, 84S582; 89JHC1061). Under the latter conditions water was eliminated from the addition products **543** to yield condensation products **544** (89JHC1061). The exo double bond of 9-benzylidene-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidine-3-carboxylates **544** could not be isomerized thermally or in the presence of a base to afford 9-benzyl-6,7-dihydropyrido[1,2-a]pyrimidine derivatives **545** (89JHC1061).

The stereochemistry of both the addition and condensation products was investigated (89JHC1061). Only the formation of *erythro* isomers could be detected in the case of the addition products. But from the 6- and 8-methyl derivatives only the *cis* isomers of **543** (R = 6-Me, 8-Me) could be isolated, and from 7-methyl derivative **541** (R = 7-Me) a 4:1 mixture of *cis* and *trans* addition products **543** (R = 7-Me) was obtained.

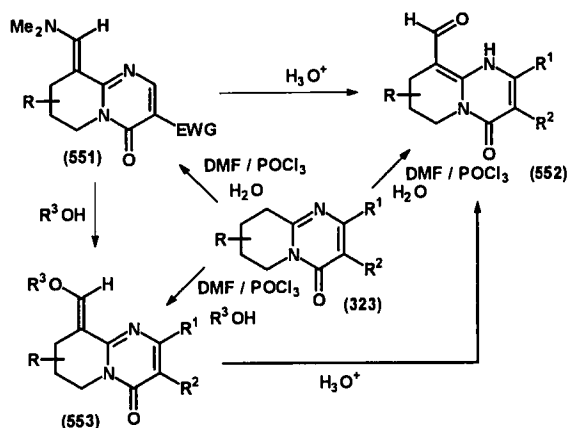
Addition of bromine in dichloromethane or of thioacetic acid in ethanol onto the methylene group of 9-arylidene and 9-carboxymethylene moieties of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines **546** stereoselectively gave 9-substituted 6,7,8,9-tetrahydro derivatives **547** and **548**, respectively, at ambient temperature (Scheme 34) (90JHC247). Addition was also stereoselective with respect to the C(9) and C(9)—C centers, giving the *erythro* diastereomers as the primary products, which may then undergo epimerization to the *threo* isomers. The structure and epimerization of the products were studied by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and by molecular mechanics calculations.



SCHEME 34

Reaction of 9-(carboxymethylene)tetrahydropyridopyrimidin-4-one **546** (R = COOH) and 2-aminothiophenol gave 9-(benzothiazin-2-yl)tetrahydropyridopyrimidin-4-one **550** as a mixture of *erythro* and *threo* isomers (90JHC247). The addition was accompanied by spontaneous cyclization between the amino and carboxyl group of intermediate **549** to the yield 9-(benzothiazin-2-yl) moiety.

6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **323** could be acylated at position 9 with Vielsmeier-Haack reagents [83JCR(S)161, 83JCS(P1)369; 85JCS(P2)1873, 85JHC593]. When an electron-withdrawing group was present at position 3 of tetrahydropyridopyrimidin-4-ones **323**, 9-dimethylaminomethylene-6,7,8,9-tetrahydro derivatives **551** were isolated from a mixture of phosphoryl chloride-dimethylformamide. In the case of other tetrahydropyridopyrimidin-4-ones, the primary products were 9-dimethylaminomethylenetetrahydropyridopyrimidines **551**, which were hydrolyzed under the work-up conditions to give 9-formyl-1,6,7,8-tetrahydropyridopyrimidin-4-ones **552** (Scheme 35) [83JCS(P1)369; 85JCS(P2)1873]. Depending upon the reaction circumstances, 3-unsubstituted tetrahydropyridopyrimidin-4-ones gave 3-unsubstituted 9-formyl-1,6,7,8-tetrahydropyridopyrimidin-4-ones **552** (R<sup>2</sup> = H) (at lower temperature with shorter reaction period) and 3-formyl-9-dimethylaminomethylene-6,7,8,9-tetrahydropyridopyrimidin-4-ones **551** (EWG = CHO) (at higher temperature with longer reaction period) [83JCS(P1)369;



SCHEME 35

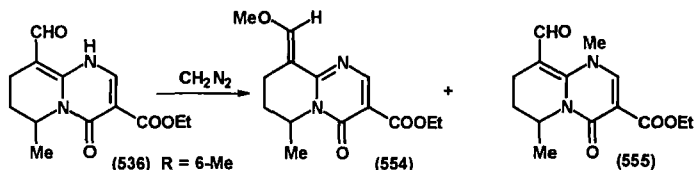
84JMC1253]. In the first step of the reaction, 3-unsubstituted 9-dimethylaminomethylene-6,7,8,9-tetrahydropyridopyrimidin-4-one formed and the electron-donating dimethylamino group activated position 3 of the pyridopyrimidinone ring for further reaction [83JCS(P1)369].

When a mixture of dimethylformamide–phosphoryl chloride was treated with an alcohol, 9-alkoxymethylene derivatives **553** could be isolated [83JCS(P1)369]. 9-Alkoxymethylene derivatives **553** were also obtained from 9-dimethylaminomethylenetetrahydropyridopyrimidin-4-ones **551** by treatment of an alcohol in the presence of hydrogen chloride [83JCS(P1)369; 85JCS(P2)1873], and from 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones **323** with a mixture of triethyl orthoformate and acetic anhydride [83JCS(P1)369]. 9-Dimethylaminomethylene derivatives **551** were also prepared from 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones **323** with dimethylformamide diethyl acetal [83JCS(P1)369]. Both 9-dimethylaminomethylene and 9-alkoxymethylene groups can be hydrolyzed to the formyl group by stirring in dilute aqueous hydrochloric acid [83JCS(P1)369; 84JMC1253; 85JCS(P2)1873].

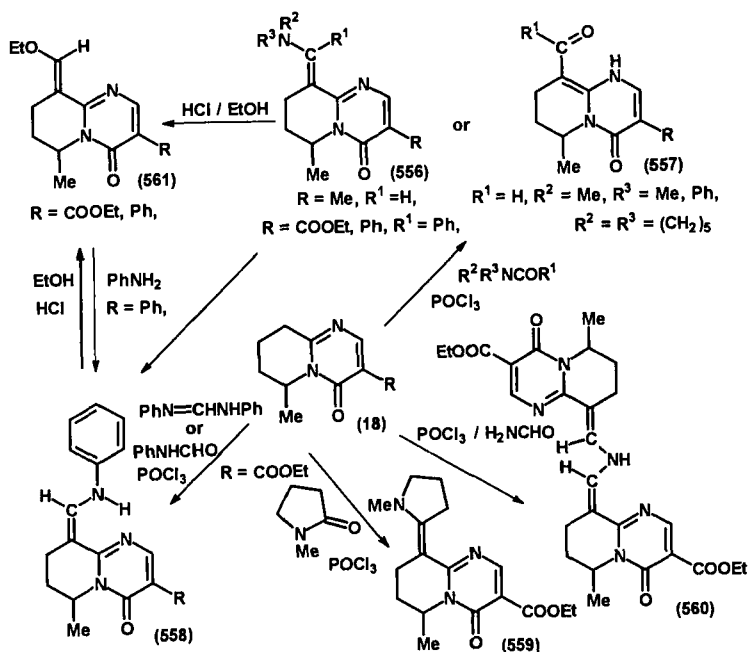
During formylation, the 2-methoxy group of tetrahydropyridopyrimidin-4-ones was exchanged for a chloro atom and the 3-carboxamido group for a 3-cyano group. Depending upon the reaction temperature, the *N*-methyl-substituted 3-carboxamido group gave the 3-CONHMe or 3-CON(CHO)Me group, and the carbohydrazido group gave the CONHN=CHNMe<sub>2</sub> or carboxyl group [83JCS(P1)369].

Reaction of 9-formyltetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one **536** ( $\text{R} = 6\text{-Me}$ ) in chloroform with an ethereal solution of diazomethane at  $-10^\circ\text{C}$  for 2 hours gave 9-methoxymethylenetetrahydropyridopyrimidin-

4-one **554** and 1,6-dimethyl-9-formyltetrahydropyridopyrimidin-4-one **555** in 54% and 4% yields, respectively, after TLC separation [85JCS(P2)1873, 85JCS(P2)1881]. The product **555** was also prepared from quaternary salt **1** by a mixture of phosphoryl chloride–dimethylformamide at 60°C in 62% yield.



6-Methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **18** reacted with the iminium salt formed *in situ* from *N*-formylpiperidine, *N*-methylformanilide, *N,N*-diethylbenzamide, and phosphoryl chloride in 1,2-dichloroethane to yield 9-aminomethylene-6,7,8,9-tetrahydro or 9-acyl-1,6,7,8-tetrahydropyridopyrimidin-4-ones **556** and **557** (Scheme 36) (85JHC593). The iminium salt formed from *N,N*-diethylacetamide and *N,N*-ethylisobutyramide was unreactive under the above reaction condi-



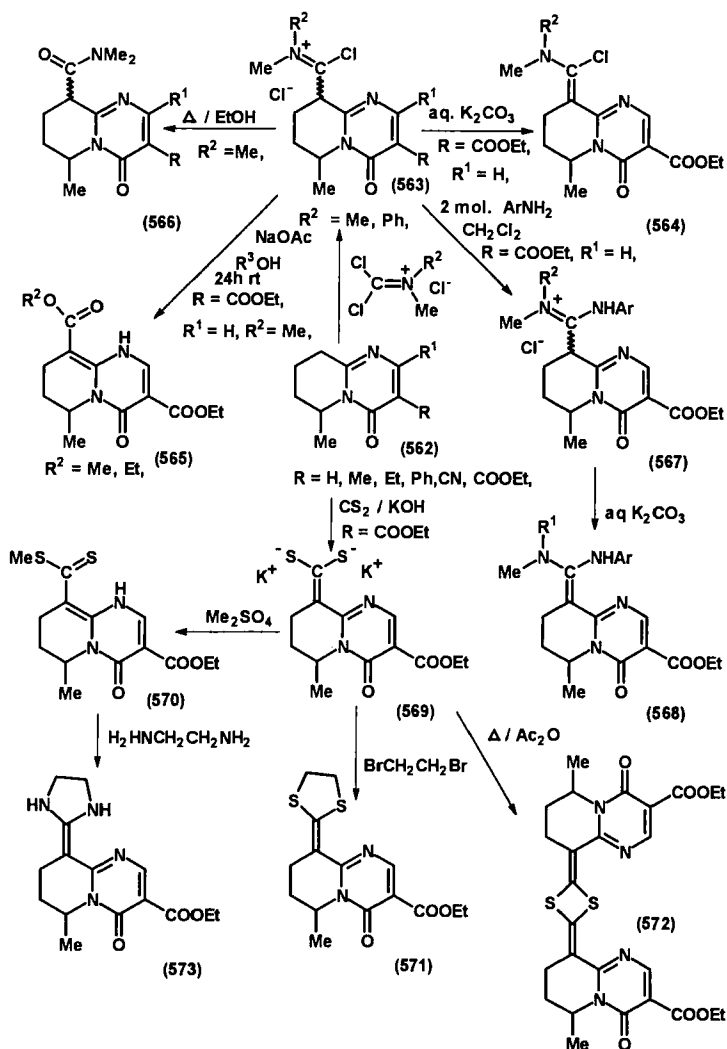
SCHEME 36

tions. The iminium salt formed from formanilide, *N*-methylpyrrolidinone, or formamide reacted only with those tetrahydropyridopyrimidin-4-ones (**18**: R = COOEt, CN) that contain a strong electron-withdrawing substituent in position 3 to afford aminomethylene derivatives **558–560**. Formamide gave bis product **560** in an excess of the reagent at 80–85°C for 4 hours in 15% yield. The 9-phenylaminomethylene group also could be introduced using *N,N'*-diphenylformamidine or in a one-pot reaction with aniline and triethyl orthoformate. The 9-*N*-methyl-*N*-phenylaminomethylene group could be converted to a 9-ethoxymethylene group by treatment with boiling ethanol containing hydrogen chloride. 9-Ethoxymethylene derivative **561** (R = Ph) reacted with aniline at 100–110°C for 1 hour to afford 9-phenylaminomethylene derivative **558** (R = Ph).

The 9-formyl- and 9-benzoyltetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones derivatives exist predominantly as the 1,6,7,8-tetrahydro tautomer stabilized by an internal hydrogen bridge between N(1) and the 9-carbonyl group [83JCS(P2)1153; 85JHC593].

Iminium chlorides **563** were prepared in the reaction of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **562** and phosgene iminium chloride in boiling dichloromethane in good yields (79NEP79/3401; 82OMR229, 82USP4321377; 83MIP1). The treatment of iminium chloride **563** (R = COOEt, R<sup>1</sup> = H) with aqueous potassium carbonate afforded 9-[chloro(dimethylamino)methylene] derivative **564**, while sodium acetate at room temperature for 24 hours gave 3,9-diester **565** (79NEP79/3401; 82USP4321377; 83MIP1). Boiling an ethanolic solution of iminium chloride **563**, or allowing **563** to stand in acetone overnight at ambient temperature, resulted in the formation of a diastereomeric mixture of 9-dimethylaminocarbonyl derivatives **566** (79NEP79/3401; 82OMR229, 82USP4321377; 83MIP1). Reaction of iminium chloride **563** (R = COOEt, R<sup>1</sup> = H) with 2 equivalents of aromatic amines or ammonia afforded 9-amidinium salts **567**, from which the free bases **568** were liberated on treatment with aqueous potassium carbonate (Scheme 37) (79NEP79/3401; 82USP4321377; 83MIP1; 85H1093).

When tetrahydropyridopyrimidine-3-carboxylate **562** (R = COOEt, R<sup>1</sup> = H) was treated with carbon disulfide in the presence of potassium hydroxide at 25–30°C, salt **569** was obtained in good yield (79NEP79/3401; 82USP4321377). The alkylation of **569** with dimethyl sulfate and with ethylene dibromide in ethanol afforded 9-dithioester **570** and 9-(dithiolen-2-ylidene) derivative **571**, respectively. When **569** was heated in acetic anhydride for 2 hours, bis product **572** was obtained in 57% yield. 9-Imidazolidine derivative **573** was prepared from both iminium chloride **563** (R = COOEt, R<sup>1</sup> = H, R<sup>2</sup> = Me) and 9-dithioester **570** by treatment with ethylenediamine (Scheme 37) (79NEP79/3401; 82USP4321377; 83MIP1).

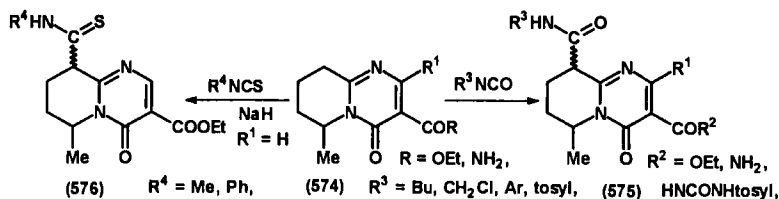


SCHEME 37

The active methylene group of tetrahydropyrido[1,2-*a*]pyrimidin-4-ones **574** smoothly reacted with isocyanates on heating in the absence of solvent or in dichloromethane to give diastereomeric mixtures of 9-carboxamide derivatives **575**. Reactions with thioisocyanates were carried out in boiling benzene in the presence of sodium hydride to give 9-thiocarboxamides **576** (79NEP79/4301; 82USP4321377; 83MIP1).

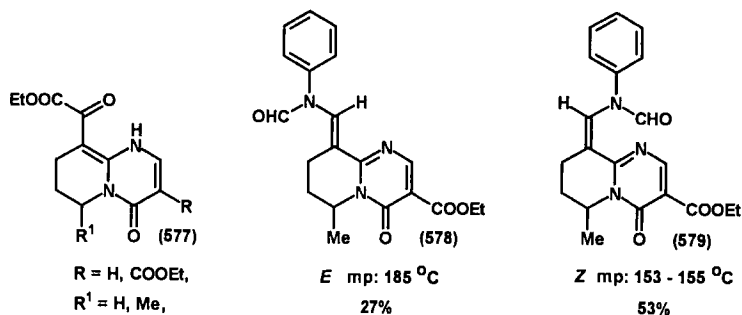
6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **528** (R = H,





COOEt;  $R^1 = \text{H, Me}$ ) were acylated with diethyl oxalate in diethyl ether in the presence of sodium ethylate at 0–20°C [89JCS(P2)1613]. After the acidification of the reaction mixture, 9-(ethoxycarbonyl)carbonyl derivatives **577** were obtained from the sodium salts. The 9-(ethoxycarbonyl)carbonyl derivatives **577** exist as 1,6,7,8-tetrahydro tautomers.

9-Arylaminomethylene-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones **34** ( $X = \text{CH}$ ) were prepared in the reaction of 9-(dimethylaminomethylene)tetrahydropyridopyrimidinones **551** and amines in boiling ethanol for 3 hours or in acetic acid at room temperature for 24 hours and in the reaction of 9-formyltetrahydropyridopyrimidinones **552** and amines in acetic acid at ambient temperature for 24 hours [83JCR(S)161, 83JCS(P2)165, 83JMC1494; 84JMC1253].

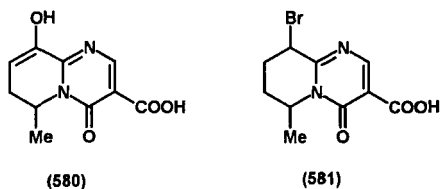


Vielsmeier–Haack formylation of 9-(phenylaminomethylene)-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one **558** ( $R = \text{COOEt}$ ) with a mixture of phosphoryl chloride–dimethylformamide at room temperature for 10 hours gave an *E*–*Z* mixture (**578** and **579**) of the 9-(*N*-phenyl-*N*-formylamino)methylene derivative (91H1455). While 9-phenylaminomethylene derivative **558** ( $R = \text{COOEt}$ ) exhibited a solvent-dependent *E*–*Z* geometric isomerism, the presence of a formyl group on the amino moiety of **558** ( $R = \text{COOEt}$ ) leads to an increase in the activation energy for isomerization around the  $\text{C}=\text{C}(9)$  double bond, thereby permitting the separation of the *E* and *Z* isomers (**578** and **579**) of the formylated product.

Antiallergic 9-(het)arylhydrazino-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]

pyrimidin-4-ones **34** ( $X = N$ ) were prepared from 9-unsubstituted 6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-ones **323** (82JMC1140; 83JMC1126, 83OMR687, 83URP999973; 84USP4461769), 9-dimethylamino-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **551** [83-JCR(S)161; 84JMC1253], and 9-formyl-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **552** (83OMR687, 83URP999973; 84JMC1253) with (het)aryldiazonium chloride in the presence or absence of sodium acetate in water or in aqueous acetic acid at 0°C.

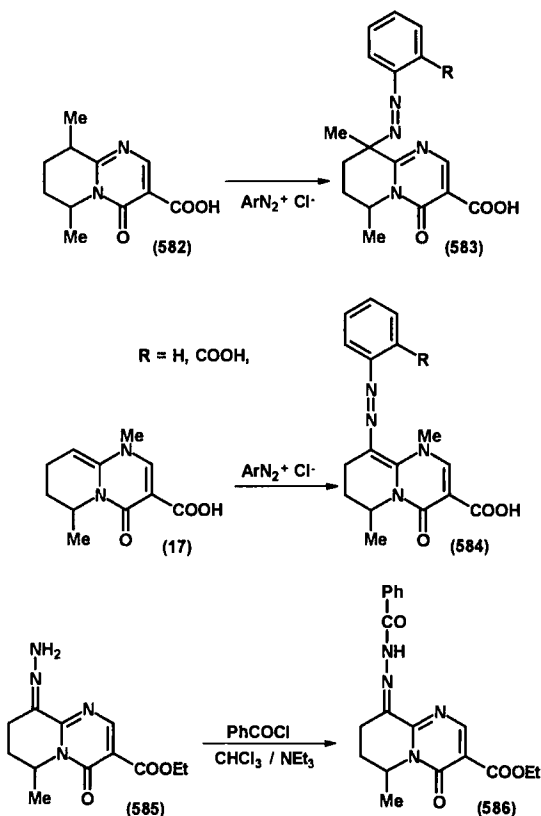
9-Arylhydrazonotetrahydropyridopyrimidin-4-ones **34** ( $X = N$ ,  $R = Me$ ,  $R^1 = aryl$ ,  $R^2 = H$ ,  $R^3 = COOH$ ) were also prepared from 9-hydroxy-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid **580** (83JMC1126, 83URP999973; 84USP4461769; 85ACH305) and from 9-bromo-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid **581** with hydrazines in alcohol at ambient temperature for 24 hours or at reflux for 2 hours (83JMC1126, 83URP999973; 84USP4461769). In the latter case an osazone-like reaction occurred (91MI2).



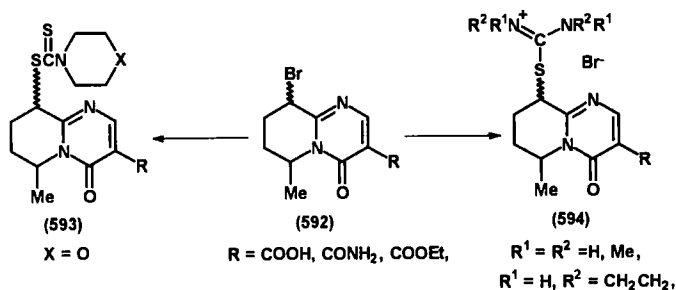
Reaction of aryldiazonium chlorides with sodium 6,9-dimethyl-6,7,8,9-tetrahydro- and 1,6-dimethyl-1,6,7,8-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **582** and **17** in water in the presence of sodium acetate at 5°C gave 9-(aryldiazo) derivatives **583** and **584** (83JMC1126).

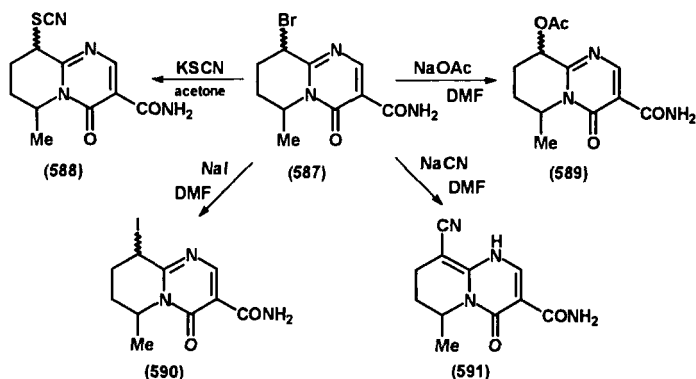
The amino moiety of the hydrazono group of 9-hydrazonopyrido[1,2-*a*]pyrimidine-3-carboxylate **585** was acylated with benzoyl chloride to give 9-benzoylhydrazono derivative **586** (83OMR687, 83URP999973; 84USP4461769). Reaction of 9-hydrazonopyrido[1,2-*a*]pyrimidine-3-carboxylate **585** with benzaldehydes in dimethyl sulfoxide at ambient temperature or in boiling ethanol or acetonitrile gave mixtures of 9-benzylidenehydrazono-6,7,8,9-tetrahydro and 9-benzylidenehydrazino-6,7-dihydro derivatives **36** (83URP999973; 84USP4461769; 91JHC781). The isomers of benzaldehyde derivative **36** ( $R = H$ ) were separated (see also Section II).

Reaction of 9-bromotetrahydropyridopyrimidine-3-carboxamide **587** with potassium thiocyanate (85H2289), sodium acetate, sodium iodide, and sodium cyanide (87H869) afforded diastereomeric mixtures of 9-thiocyanato **588**, 9-acetoxy **589**, 9-iodo-6,7,8,9-tetrahydro **590**, and 9-



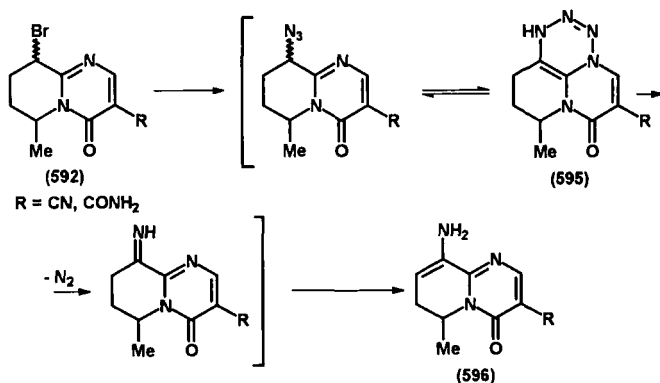
cyano-1,6,7,8-tetrahydro derivatives **591**, respectively (Scheme 38). Reaction of 9-bromotetrahydropyrido[1,2-*a*]pyrimidin-4-ones **592** with sodium dithiocarbamates and thiocarbamides in acetone at ambient temperature gave 9-dithiocarbamates **593** and isothiuronium salts **594**, respectively (87H869).



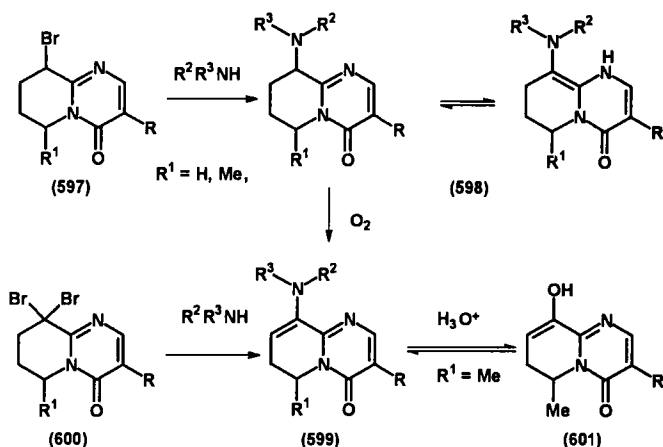


SCHEME 38

9-Amino-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidines **596** were prepared from 9-bromotetrahydropyridopyrimidin-4-ones **592** with sodium azide in acetone at 25°C in 42–55% yields (85TL3621). Considering the very mild reaction conditions, a cyclic intermediate **595** was suggested instead of a nitrene intermediate.



Reaction of 9-bromotetrahydropyridopyrimidin-4-ones **597** with amines in a solvent at ambient or reflux under an inert atmosphere (e.g., argon) afforded 9-aminotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **598** [83JCS(P2)1413, 83JMC1494; 85JCS(P1)1015], which exhibit a solvent-dependent imine–enamine tautomerism (Scheme 39; see also Section II) [85JCS(P1)1015]. If these reactions were carried out in an open vessel, *N*-alkylation and oxidation also took place to give 9-amino-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **599** (83JMC1494; 85JHC1253). 9-



SCHEME 39

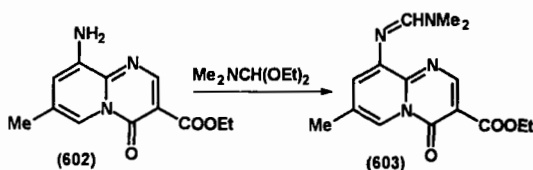
Amino-6,7-dihydro-4H-pyrimido[1,2-a]pyrimidin-4-ones **599** could also be prepared as follows: (1) from 9-aminotetrahydropyrido[1,2-a]pyrimidin-4-ones **598** when atmospheric oxygen was bubbled through their solutions; (2) in the reaction of 9,9-dibromotetrahydropyrido[1,2-a]pyrimidin-4-ones **600** and amines in a solvent in the presence or absence of an acid acceptor at room temperature or at elevated temperature (81GEP3017560; 83JMC1494, 83OMR687; 85JHC1253); (3) in the reaction of 9-hydroxy-6,7-dihydro-4H-pyrido[1,2-a]pyrimidine-4-ones **601** and an aniline in boiling ethanol (83JMC1494; 85JHC1253).

9-Hydroxy-6-methyl-6,7-dihydro-4H-pyrido[1,2-a]pyrimidin-4-ones **601** were prepared by the acidic hydrolysis of 9-phenylamino-6-methyl-6,7-dihydro-4H-pyrido[1,2-a]pyrimidin-4-ones **599** ( $R^1 = Me$ ,  $R^2 = Ph$ ,  $R^3 = H$ ) in dilute hydrochloric acid at room temperature for 2 days in 27–70% yields (83JMC1494; 85JHC1253).

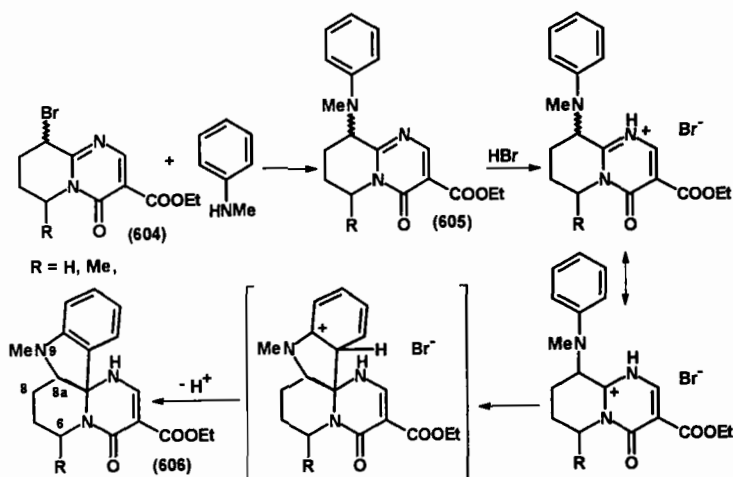
The reaction of the 9-amino group of 4H-pyrido[1,2-a]pyrimidin-4-one **602** with *N,N*-dimethylformamide diethyl acetal in boiling acetone afforded 9-(*N,N*-dimethylaminomethylene)amine derivative **603** (91H1455).

#### 10. Cyclization Involving Position 9a and the 9-Substituent of the Pyrido[1,2-a]pyrimidin-4-ones

Tetracyclic pyrimido[1',2':1,2]pyrido[3,1-b]indole derivative **606** ( $R = H$ ) was obtained when 9-bromotetrahydropyrido[1,2-a]pyrimidin-4-one **604** ( $R = H$ ) reacted with *N*-methylaniline in boiling ethanol for 8 hours under nitrogen in 37% yield (Scheme 40) (91JHC1405). In the reac-



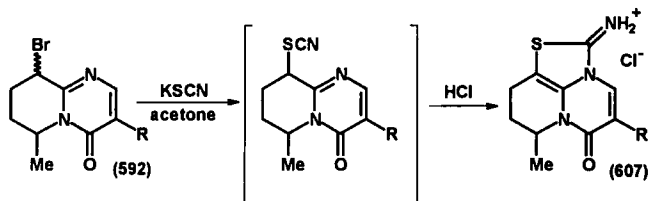
tion of 9-bromo-6-methyltetrahydropyridopyrimidin-4-one **606** ( $R = \text{Me}$ ) and *N*-methylaniline in acetonitrile at room temperature for 3–6 days under argon, 9-aminotetrahydropyridopyrimidone **605** ( $R = \text{Me}$ ), which exhibits imine–enamine tautomerism, could be isolated in 50% yield [85JCS(P1)1015]. When 6-methyl derivative **605** ( $R = \text{Me}$ ) stood in a mixture of glacial acetic acid and 85% phosphoric acid or in ethanol containing 20% hydrogen chloride at ambient temperature for 3 days, tetracyclic derivative **606** ( $R = \text{Me}$ ) was obtained in 40% and 60% yield, respectively (91JHC1405). According to the reaction mechanism suggested in Scheme 40, after the nucleophilic replacement of the 9-bromine atom, protonation in N-1 takes place, and then a new bond develops between the electron-deficient C(9a) carbon and one of the relatively electron-rich *ortho* carbons of the phenyl ring. Finally, rearomatization of the phenyl ring results in the formation of the tetracyclic derivatives **606**. X-Ray investigation of desmethyl derivative **606** ( $R = \text{H}$ ) revealed that the annelation of the pyrimidine and piperidine ring is *transoid*, while that of the piperidine ring and pyrroline ring is *cis*, and the piperidine ring adopts an unusual  ${}^6T_8$  twisted boat conformation, while the pyrroline ring has a  ${}^6T_{8a}$  conformation.



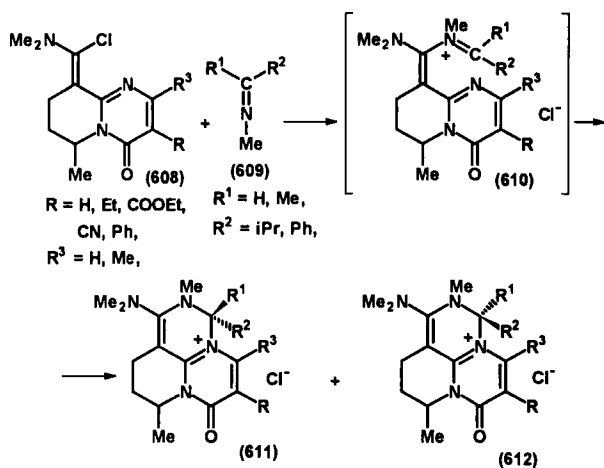
SCHEME 40

### 11. Cyclization Involving the *N*-1 Atom and the 9-Substituent of Pyrido[1,2-*a*]pyrimidin-4-ones

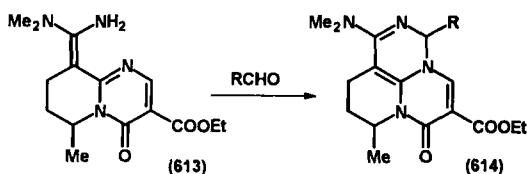
9-Bromotetrahydropyridopyrimidin-4-ones **592** reacted with potassium thiocyanate at 25°C and the reaction mixtures were treated with an equimolar amount of aqueous hydrochloric acid to afford hydrochlorides of tricyclic 1-thia-2a,5a-diazaacenaphthenes **607** were obtained (85H2289).



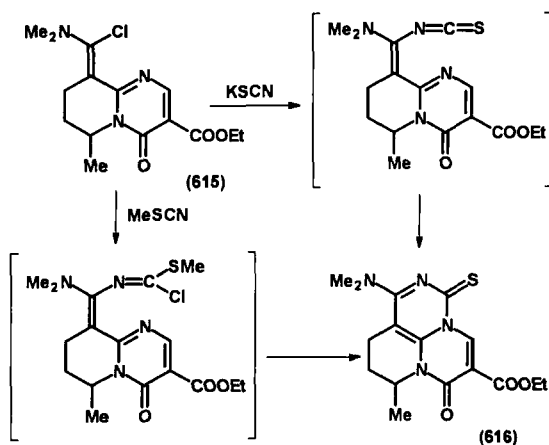
Reaction of 9-[chloro(dimethylamino)methylene]tetrahydropyrido[1,2-*a*]pyrimidin-4-ones **608** and aldimines or ketimines **609** in chloroform and acetonitrile gave a diastereomeric mixture of tricyclic compounds **611** and **612** at room temperature (82BEP892120, 82TL2891). The formation of compound **610** and the formation of a 1 : 1 mixture of the tricyclic products **611** and **612** could be detected by  $^1\text{H}$  NMR spectroscopy (82TL2891). After refluxing the reaction mixtures, only the thermodynamic product **611** could be isolated in pure form. 9-[Chloro(dimethylamino)methylene] 9-[Chloro(dimethylamino)methylene] derivatives **608** ( $\text{R} = \text{CN}, \text{COOEt}$ ) also reacted with cyclic imines to yield the corresponding tetra- and pentacyclic quaternary salts, similar to **611** and **612** (87H2615).



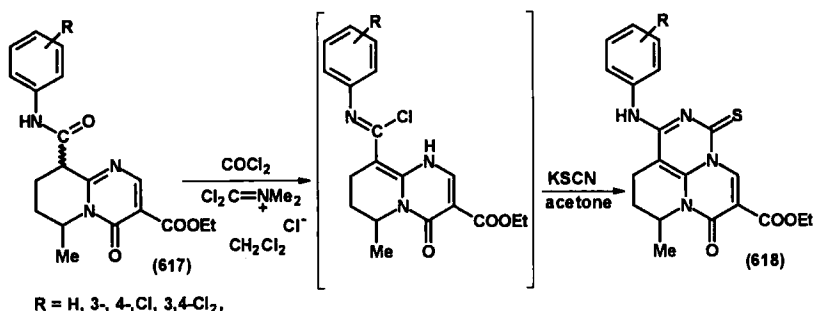
Tricyclic derivatives **614** were also prepared in the reaction of 9-[amino(*N,N*-dimethylamino)methylene] derivative **613** with 38% aqueous formaldehyde in dichloromethane at room temperature for 12 hours, and with other aldehydes in boiling ethanol for 5–10 hours (85H1093). According to  $^1\text{H}$  NMR investigations, only single stereoisomers were formed.



6-Oxo-2,3a,6a-triazaphenalene-3-thione **616** was obtained from 9-[chloro(*N,N*-dimethylamino)methylene]tetrahydropyridopyrimidin-4-one **615** both with potassium thiocyanate in acetone at room temperature for 24 hours and with methyl thiocyanate in boiling dichloromethane for 4 hours (85H1167). The hard electrophile  $\alpha$ -chloroenamine **615** reacted with the hard nucleophilic site of the thiocyanate group. Formation of *S*-substituted derivatives was not observed. Further 6-oxo-2,3a,6a-triazaphenalene-3-thiones **618** were also prepared when 9-aminocarbonyltetrahydropyrido[1,2-*a*]pyrimidinones **617** were reacted first with phosgene or phosgene dichloromethylenedimethyliminium chloride and then the evaporated reaction mixtures were treated with potassium thiocyanate at room temperature (85H1167).

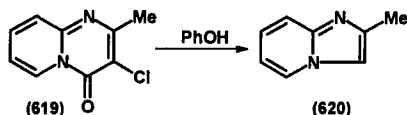




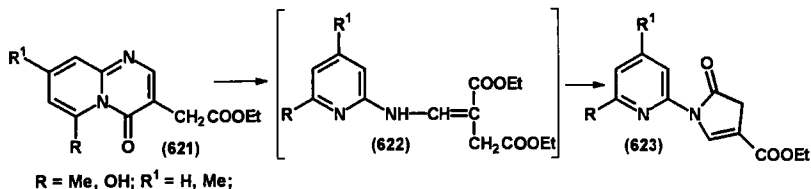


## 12. Ring Transformation

The treatment of 3-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **619** with sodium phenolate in boiling ethanol yielded 2-methylimidazo[1,2-*a*]pyrimidine **620** instead of the chloro-to-phenoxy exchange reaction (83H1083).



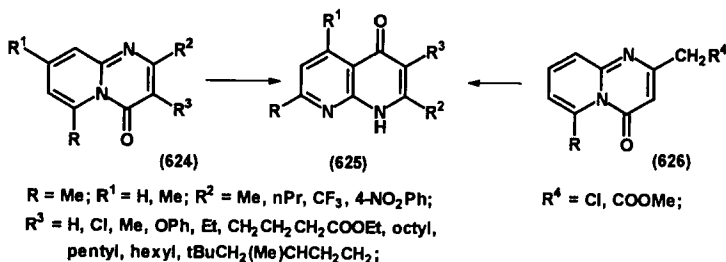
When 6-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetates **621** were left to stand in ethanol in the presence of sodium ethylate at ambient temperature for 10 minutes, 1-(2-pyridyl)pyrrolinones **623** were isolated in 63–68% yields [84JCS(P1)1799]. In the first step, ring opening occurred on the action of ethylate ion on the ring carbonyl of compound **621**, followed by ring closure between the amino and nonconjugated ester groups of the ring-opened intermediate **622** to give 1-(2-pyridyl)pyrrolinone **623**.



6-Substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **624** could be thermally rearranged to 1,8-naphthyridines **625** by heating in a high-boiling solvent. As high-boiling solvent, paraffin oil at 280–350°C for 30 minutes

(82JHC1017, 82MI6; 83H1083; 87SC319; 88GEP3644825) or diphenyl ether at reflux for 4–24 hours (83JHC1053; 92MIP4) were applied.

When 2-chloromethyl and 2-(methoxycarbonylmethyl) derivatives of 6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **626** were heated in diphenyl ether for 5 hours, 2,7-dimethyl-1,8-naphthyridin-4-one **625** ( $R = R^2 = \text{Me}$ ;  $R^1 = R^3 = \text{H}$ ) was obtained in 84% and 85% yields, respectively (83JHC1053). The heating of the 2-(ethoxycarbonylpropyl)-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **624** ( $R = \text{Me}$ ,  $R^2 = (\text{CH}_2)_3\text{COOEt}$ ,  $R^1 = R^3 = \text{H}$ ) in paraffin oil yielded the 2-(ethoxycarbonylpropyl) derivative of 1,8-naphthyridine **625** ( $R = \text{Me}$ ,  $R^2 = (\text{CH}_2)_3\text{COOEt}$ ,  $R^1 = R^3 = \text{H}$ ) (87SC319).

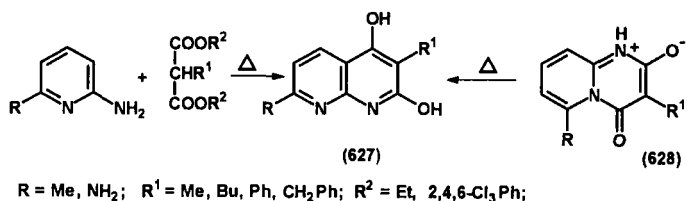


Investigating the role of the substituent at position 3 of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, it was found that the resonance effect of the 3-substituent also plays a role in the ring transformation, as well as the steric property of the 6-substituent [88JCS(P2)1287].

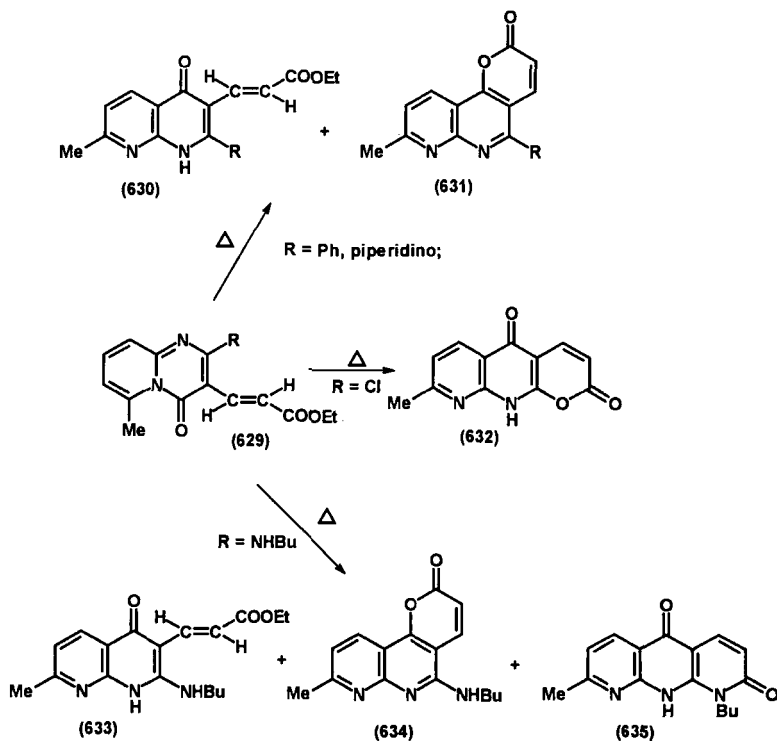
Ring transformation of the initial 6-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones also occurred when 2-[(6-substituted 2-pyridyl)acrylates were heated in a high-boiling solvent. For example, heating diethyl [(4,6-dimethyl-2-pyridyl)amino]malonate in boiling diphenyl ether afforded ethyl 5,7-dimethyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (92MIP4). Similarly, other 7-substituted-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylates were also prepared (93MI1).

1,8-Naphthyridine-2,4-diol **627** were prepared when 2-amino-6-methyl- and 2,6-diaminopyridine reacted with diethyl malonate or bis(2,4,6-trichlorophenyl) malonate in a melt at 220–250°C or in boiling diphenyl ether (88JHC1231). 1,8-Naphthyridine-2,4-diols **627** were also obtained by the thermal isomerization of 6-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **628** by heating in a melt at 205–225°C for 15–30 minutes, refluxing in nitrobenzene for 3 minutes, or by sublimation *in vacuo* at 14–20 mmHg.

Ring transformation of 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates **629** was investigated using boiling Dowtherm A (Scheme 41)

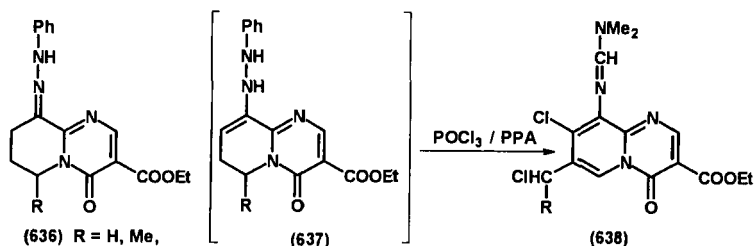


(92JHC559). When 2-phenylpyridopyrimidine-3-acrylate **629** (R = Ph) was added to refluxing Dowtherm A and the reaction period was 5 hours, 1,8-naphthyridine-3-acrylate **630** (R = Ph) and 2*H*-pyrano[3,2-*c*][1,8]naphthyridin-2-one **631** (R = Ph) were prepared in 70% and 1.7% yields, respectively. 2-Piperidinopyridopyrimidine-3-acrylate **629** (R = piperidino) afforded 1,8-naphthyridine-3-acrylate **630** (R = piperidino) and tricyclic **631** (R = piperidino) in 63% and 15% yields, respectively, when the reaction period was 20 minutes. After 90 minutes, only



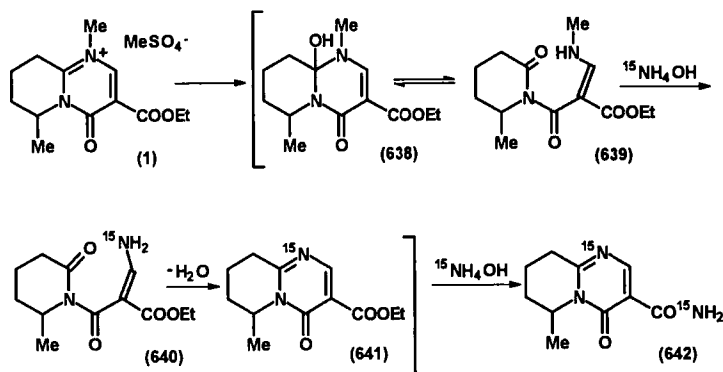
SCHEME 41

angularly annelated tricyclic **631** (R = piperidino) was obtained in 66% yield. Further heating of 1,8-naphthyridine-3-acrylate **630** (R = piperidino) yielded pyrano(3,2-*c*)[1,8]naphthyridin-2-one **631** (R = piperidino). Heating 2-chloropyridopyrimidine-3-acrylate **629** (R = Cl) in Dowtherm A at 255°C for 5 hours afforded linearly annelated pyrano[2,3-*b*][1,8]naphthyridine-2,5-dione **632** in 58% yield. When the latter reaction was carried out in Marlotherm at 320°C for 25 minutes, tricyclic **632** was obtained in 73% yield. From the tarry reaction mixture of 2-butylaminopyridido[1,2-*a*]pyrimidine-3-acrylate **629** (R = *n*BuNH) in Dowtherm A after 50 minutes, 1,8-naphthyridine-3-acrylate **633**, pyrano[3,2-*c*][1,8]naphthyridin-2-one **634**, and anthyridine-2,5-dione **635** were isolated in 1.8%, 6.1%, and 14.1% yields, respectively.



Vilsmeier-Haack formylation of 9-phenylhydrazonotetrahydropyrido[1,2-*a*]pyrimidin-4-ones **636** with a mixture of phosphoryl chloride and dimethylformamide at 60°C for 2 hours, then at 90°C for 0.5 hour, led to the formation of unsaturated dichlorinated 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **331** (91H1455). Because the analog 9-(phenylaminomethylene)tetrahydropyrido[1,2-*a*]pyrimidin-4-one **558** (R = COOEt) did not give a similar product, it was assumed that the 6,7-dihydro form **637** was involved in the ring transformation.

6-Methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide **642** labeled with <sup>15</sup>N isotope both in position 1 and in the carboxamido group was obtained in 42% yield when a solution of quaternary salt **1** was left to stand for 3 days at ambient temperature in 20% ammonium hydroxide labeled with <sup>15</sup>N isotope (85JOC2918) (Scheme 42). In the first step pseudo-base **638** was formed by nucleophilic addition of hydroxyl ion to the C=N double bond, then ring opening occurred, followed by trans-amination of the enamine **639** and by ring closure of intermediate **640** to give 6,7,8,9-tetrahydropyridopyrimidine-3-carboxylate **641**. Finally, the amidation of the 3-carbethoxy group occurred to yield compound **642**.



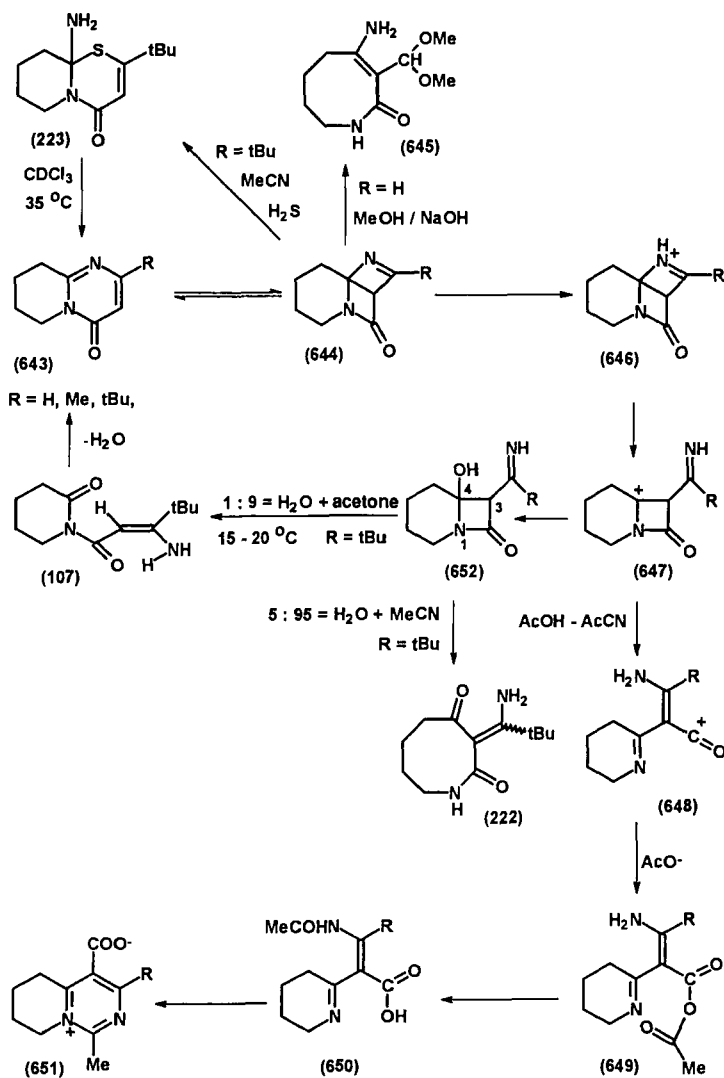
SCHEME 42

### 13. Photochemical Reactions

Yamazaki and co-workers investigated the photochemistry of different pyrimidin-4(3*H*)-ones, among them 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **643** [83JOC2914, 83TL5237; 85JOC166, 85TL3247; 87JOC2455; 88JCS(P1)2653; 89JCS(P1)1231]. Irradiation of tetrahydropyrido[1,2-*a*]pyrimidin-4-one **643** (*R* = *H*) in methanol at  $-10^\circ\text{C}$  for 7 hours gave eight-membered lactam **645** in 1.8% yield (Scheme 43) (83JOC2914). The yield was higher (47%) if irradiation was carried out in the presence of sodium methylate for 4.5 hours. It was suggested that lactam **645** was produced by the nucleophilic addition of methanol to the imino bond of the initial Dewar 4-pyrimidinone **644**, followed by disrotatory electrocyclic reaction.

The irradiation of 2-methyltetrahydropyridopyrimidin-4-one **643** (*R* = *Me*) in a mixture of acetic acid and acetonitrile under argon at  $25^\circ\text{C}$  afforded betaine **651** (*R* = *Me*) in 57% yield (83TL5237; 87JOC2455). Upon the formation of betaine **651** after the protonation of the imino nitrogen of the Dewar pyrimidinone **646**, ring opening yielded azetidiny cation **647**. The ring opening of the azetidiny cation **647** afforded acyl cation **648**, which reacted with acetoxo anion to yield a mixed anhydride **649**. Then migration of the acetyl group to the amino group **650** and ring closure gave betaine **651**. An experiment with  $^{13}\text{C}$ -labeled acetic acid and a Dewar pyrimidinone obtained from 2,3,6-trimethylpyrimidin-4(3*H*)-one indicated that the two carbons of acetic acid were incorporated between the nitrogen atoms of the betaines.

The Dewar pyrimidinone **644** (*R* = *t*Bu) could be isolated in 16% yield when 2-*tert*-butyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **643**



SCHEME 43

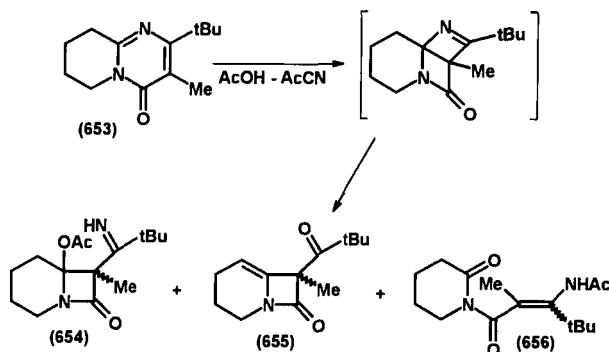
(R = *t*Bu) was irradiated in a mixture of liquid ammonia and diethyl ether at  $-40^\circ\text{C}$  for 5 hours [85JOC166; 89JCS(P1)1231]. The solvolysis of the Dewar isomer **644** (R = *t*Bu) in a 1:9 mixture of water and acetone at  $15-21^\circ\text{C}$  for 2 hours afforded roughly a 1:2 mixture of ring-opened enamine **107** and pyrido[1,2-*a*]pyrimidinone **643** (R = *t*Bu) (85TL3247). Ena-

mine **107** was isolated as a hydrate. The Dewar pyrimidinone **644** ( $R = t\text{Bu}$ ) gave a 10 : 85 mixture of monocyclic eight-membered lactam **222** and pyrido[1,2-*a*]pyrimidin-4-one **643** ( $R = t\text{Bu}$ ) in acetonitrile containing 5% water at 35°C for 37 h [89JCS(P1)1231].

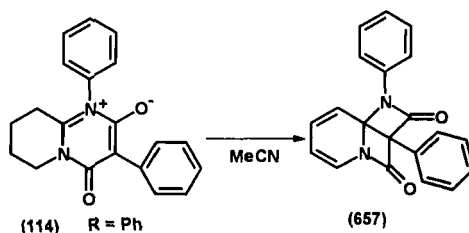
Enamine **107** and monocyclic lactam **222** were formed by the cleavage of C(3)—C(4) and N(1)—C(4) bonds of hydroxy azetidinone derivative **652**, respectively. An increase of solvent polarity alters the relative ratio of the C(3)—C(4) to N(1)—C(4) bond cleavage. Hydroxy azetidinone derivative **652** was formed from azetidinylium cation **647** by nucleophilic attack by water.

When Dewar pyrimidinone **644** ( $R = t\text{Bu}$ ) was left to stand in acetonitrile containing hydrogen sulfide at 0°C for 15–19 hours, hexahydro-4*H*-pyrido[2,1-*b*][1,3]thiazin-4-one **223** and tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **643** ( $R = t\text{Bu}$ ) were obtained in 52% and 32% yields, respectively [89JCS(P1)1231]. When pyrido[2,1-*b*][1,3]thiazine **223** was set aside for 64 hours at 35°C in  $\text{CDCl}_3$ , pyrido[1,2-*a*]pyrimidin-4-one **643** ( $R = t\text{Bu}$ ) was obtained in 95% yield. The hydrated enamine **107** in methanol at 16–23°C reverted to the bicyclic pyrido[1,2-*a*]pyrimidin-4-one **643** ( $R = t\text{Bu}$ ) after 2 days in almost quantitative yield [85JOC166, 85TL3247; 89JCS(P1)1231].

From the reaction mixture of 3-methyl-2-*tert*-butyl-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-one **653** in a 1 : 2 mixture of acetic acid and acetonitrile under argon at 0°C, after photolysis with a high-pressure mercury lamp, 6-acetoxy-1-azabicyclo[4.2.0]octan-8-one **654**, 1-azabicyclo[4.2.0]oct-5-en-8-one **655**, and piperidone derivative **656** could be isolated in 72%, 7%, and 1% yields, respectively [88JCS(P1)2653].

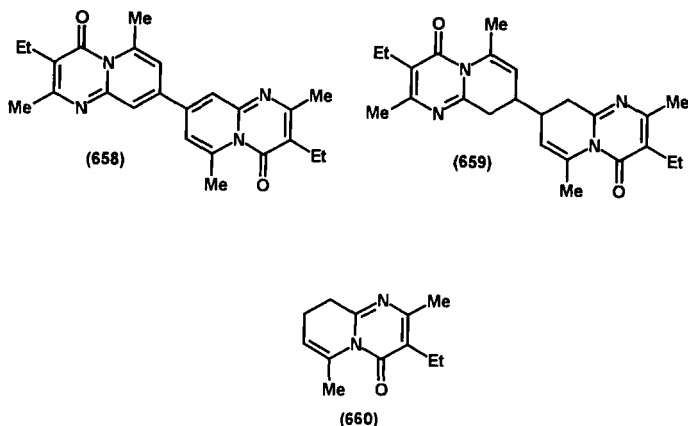


Dewar pyrimidinone **657** was obtained in 92% yield when a solution of pyrido[1,2-*a*]pyrimidin-4-one **114** ( $R = \text{Ph}$ ) in acetonitrile was irradiated with a medium-pressure mercury lamp at 20°C (86CC687).



#### 14. Electrochemical Reactions

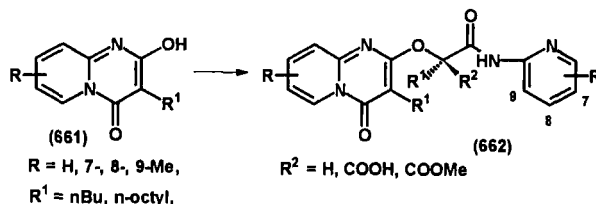
Electrochemical reactivity of 2,6-dimethyl-3-ethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **347** was investigated by Szebényi-Györy *et al.* (82MI8; 84MI4). Dimer **658** was obtained in 63% yield by preparative electrolysis of the hydrochloride salt of compound **347** using a mercury working cathode and a platinum anode separated by a diaphragm in acetonitrile with tetrabutylammonium iodide as supporting electrolyte (82MI8). When a controlled potential electrolysis was performed in a methanolic borate buffer solution at pH = 9.10 on a dropping mercury electrode with a mercury-pool cathode, at the first polarographic wave [1.45 V against a saturated calomel electrode (SCE)] dihydro dimer **659** was obtained in 52% yield (84MI4). If the electrolysis was performed in alkaline methanolic solution at pH = 13.4, at the second polarographic wave (−1.86 V against SCE) 8,9-dihydropyrido[1,2-*a*]pyrimidin-4-one **660** was obtained in 87% yield (84MI4).



Electrochemical oxidation of Chinoin-127 **19** afforded 1,6-dimethyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide **355** (87MI6).

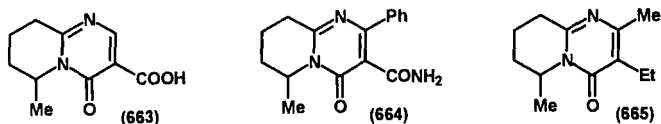


The electrochemical behavior of "malonyl- $\alpha$ -aminopyridines" **661** was investigated by Gullu *et al.* in acetonitrile or a mixture of trifluoroacetic acid and dichloromethane containing tetrabutylammonium tetrafluoroborate or triethylammonium trifluoroacetate in a water-jacketed, two-compartment glass cell equipped with a platinum disk anode at 1.50 V (Ag/Ag<sup>+</sup>) and a carbon-rod secondary electrode (91T675). Controlled potential anodic oxidation of **661** afforded labile coupled carboxylic acids **662** (R<sup>2</sup> = COOH), which easily decarboxylated to compounds **662** (R<sup>2</sup> = H) under the work-up conditions. Sometimes, the carboxylic acid **662** (R<sup>2</sup> = COOH) could be isolated; or when the reaction mixture was treated with methanol, methyl ester **662** (R = H, R<sup>1</sup> = Bu, R<sup>2</sup> = COOMe) was obtained in 40% yield.

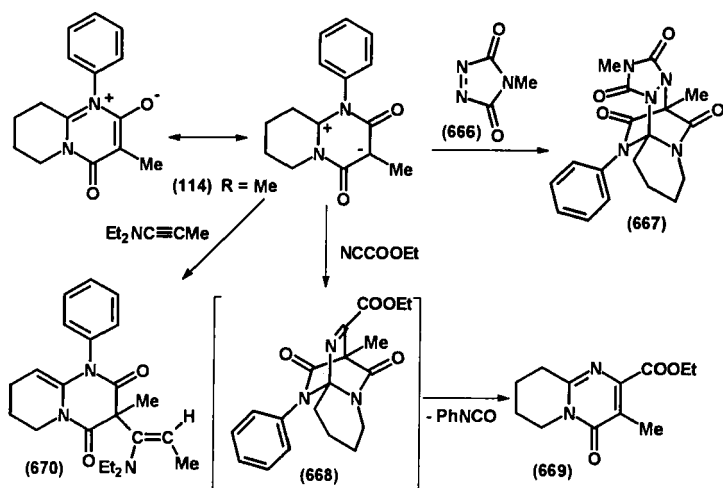


### 15. Miscellaneous Reactions

Resolution of different racemic 6-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-*a*]pyrimidin-4-ones **663**–**665** was investigated by Fogassy *et al.* by a method using two immiscible solvents and half-equivalent amounts of a resolving agent (81T3093; 85MIP2, 85T2465).



A 1,4-dipolar cycloaddition between tetrahydropyrido[1,2-*a*]pyrimidinone **114** (R = Me) and 4-methyl-1,2,4-triazoline-3,5-dione **666** gave stable adduct **667** in acetonitrile or in acetic acid at room temperature for 1 hour (Scheme 44) (85CB4567). When ethyl cyanofornate was used as dienophile in boiling toluene for 20 hours, ethyl 3-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-*a*]pyrimidine-2-carboxylate **669** was obtained (86CB1445). Pyrido[1,2-*a*]pyrimidine-2-carboxylate **669** was formed from the initial adduct **668** by elimination of phenyl isocyanate. Reaction of tetrahydropyrido[1,2-*a*]pyrimidinone **114** (R = Me) with 1-(diethylamino)-1-propyne in

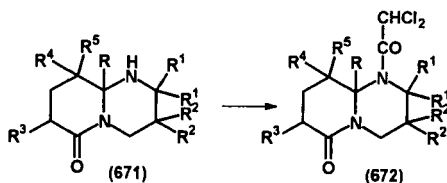


SCHEME 44

boiling toluene in the presence of hydroquinone for 16 hours afforded an adduct **670** in 31% yield (86CB3247).

#### D. 6-Oxo-2*H*-PYRIDO[1,2-*a*]PYRIMIDINES

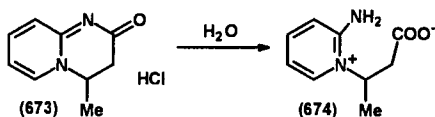
Perhydropyrido[1,2-*a*]pyrimidin-6-ones **671** were acylated with 2,2-dichloroacetyl chloride in toluene in the presence of aqueous sodium hydroxide solution or triethylamine for 12–16 hours to yield 1-(2,2-dichloroacetyl) derivatives **672** (81GEP2948535; 82EUP65724).



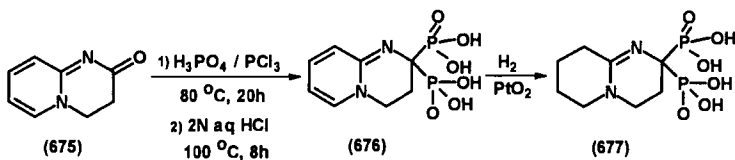
$\text{R} - \text{R}^4 = \text{H, Me}; \text{R}^5 = \text{H, Me, OMe},$

#### E. 3,4-DIHYDRO-2*H*-PYRIDO[1,2-*a*]PYRIMIDIN-2-ONES

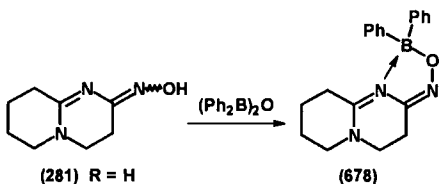
Heating the hydrochloride salt of 4-methyl-3,4-dihydro-2*H*-pyridopyrimidine **673** in a solution of sodium hydrogen carbonate gave betaine **674** (92KGS80).



The reaction of a molten mixture of 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one **675** and phosphorous acid with phosphorus trichloride, followed by treatment of the reaction mixture with 2 *N* aqueous hydrochloric acid, afforded 3,4-dihydropyridopyrimidine-2,2-diphosphoric acid **676** in 38% yield (91GEP3930130). Catalytic reduction of diphosphonic acid **676** in water over platinum dioxide gave hexahydropyrido[1,2-a]pyrimidine-2,2-diphosphonic acid **677**.

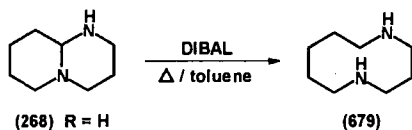


Reaction of 2-(hydroxyimino)hexahydropyrido[1,2-a]pyrimidine **281** (R = H) with diphenylboron anhydride in ethanol yielded boron complexes **678** (92AP23).



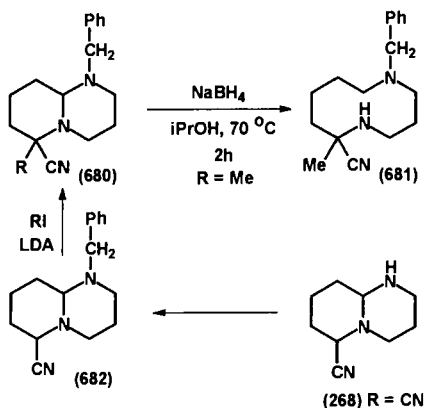
## F. PERHYDROPYRIDO[1,2-a]PYRIMIDINES

The treatment of perhydropyrido[1,2-a]pyrimidine **268** (R = H) with diisobutylaluminum hydride overnight afforded monocyclic diamine **679** (82TL4181; 93JA6580).



Reduction of 6-cyano-6-methylperhydropyrido[1,2-a]pyrimidine **680** (R = Me) with sodium borohydride afforded diazacyclodecane **681**.

[87JAP(K)87/209067]. 1-Benzyl-6-cyanoperhydropyrido[1,2-*a*]pyrimidine **682** was obtained by the alkylation of 6-cyanoperhydropyrido[1,2-*a*]pyrimidine **268** ( $R = \text{CN}$ ) with benzyl bromide in the presence of sodium hydride in dimethylformamide. The 1-benzyl-6-cyanoperhydropyrido[1,2-*a*]pyrimidine **682** was alkylated at position 6 with alkyl iodides in tetrahydrofuran at  $-78^\circ\text{C}$  in the presence of lithium diisopropylamide to afford 6-alkyl-1-benzyl-6-cyanopyrido[1,2-*a*]pyrimidines **680**.



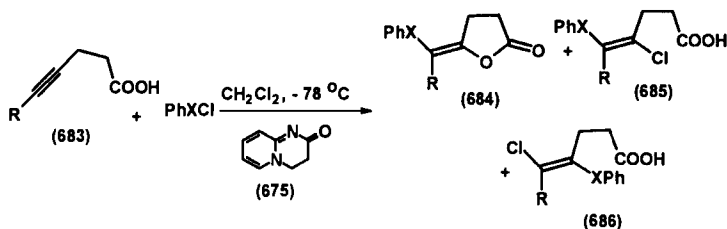
## V. Applications of Pyrido[1,2-*a*]pyrimidines

2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones have been applied in test strips for bilirubin determination in body fluids [92JAP(K)92/188068], while they and their 3,4-dihydro derivatives have served as hardening agents and post-hardening degradation inhibitors in silver halide photographic materials [81JAP(K)81/01043]. 2*H*-Pyrido[1,2-*a*]pyrimidin-2-ones have also been used in positive-working, light-sensitive compositions (92GEP4124426).

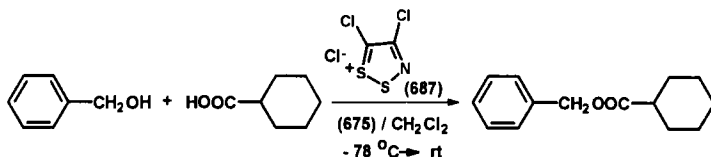
3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one **675**, a neutral hydrogen chloride acceptor, has been shown to give better yields in regio- and stereospecific thio- and selenolactonizations of hept-4-ynoic and hex-4-ynoic acids **683** with benzenesulfonyl and benzeneselenenyl chlorides than triethylamine [86JCS(P1)1999]. In the case of dihydropyrido[1,2-*a*]pyrimidinone **675**, noncyclized products **685** and **686** were formed only in trace amounts.

Benzyl cyclohexanecarboxylate was prepared in 46% yield when a solution of benzyl alcohol and cyclohexanecarboxylic acid in dichloromethane was treated with 1.2 equivalents of Appel's salt **687** in the presence of 2 equivalents of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one **675** at  $-78^\circ\text{C}$

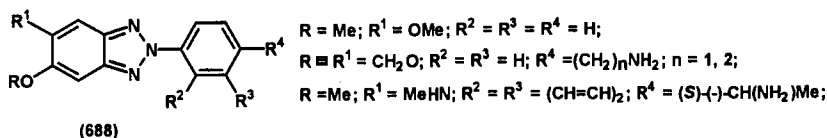
and warming to room temperature (93TL2737). Better yield (81%) could be achieved if 2,6-lutidine was used as base instead of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one **675**.



The use of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one **675** and its alkyl derivatives in test paper strips for the detection of bilirubin in body fluids, especially in urine, has been reported [83JAP(K)83/18168].



9-Methyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one is used in fluorescence (chiral) derivatization of carboxylic acids in HPLC with different 2-substituted 2*H*-benzotriazoles **688** in the presence of 2-bromo-1-ethylpyridinium tetrafluoroborate at room temperature (89MI2, 89MI15). This sensitive method has proved useful for the determination of carboxylic acids (e.g., ibuprofen) in small amounts of biological samples (89MI2).



3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one **675** has also been used in the preparation of binary photographic sensitizers as a nonbasic hydrogen halide acceptor (93EUP565074).

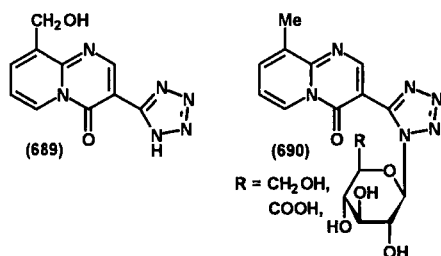
The outstanding representatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were investigated in different pharmacological and biochemical systems (see Scheme 1). Some of them have been introduced into the therapy, while others are currently under clinical investigations.

Along with that of other orally administered drugs, the nitrosatability

of rimazolium **1** was investigated at constant pH and under simulated stomach conditions (82MI11; 90MI20). The analgesic profile of rimazolium was compared to that of different classes of pain killers (88AF552), and the analgesic, antiinflammatory, and gastrointestinal effects of rimazolium, morphine, and indomethacin were investigated and compared (85MI22; 89MI19; 92MI28). Rimazolium was shown to enhance the analgesic activity of the tranquilizer gidifen (85MI8). It has been reported that the side effects of indomethacin are significantly reduced by coadministration of rimazolium in rats (83MI1). Their combination delays the appearance of the serum maximum and the elimination of indomethacin from the blood (83MI3). The unfavorable side effects of indomethacin were also mitigated in humans (83EUP91179). Investigations of the metabolic interactions of rimazolium with ethylmorphine and ethoxycoumarin have been carried out using rat liver homogenate (80MI1; 82PHA783). A method was developed to measure the color of rimazolium in injection solutions during the manufacturing process (86MI11).

The effects of antiatherosclerotic acitemat **2** were investigated in different *in vitro* and *in vivo* models (81MI5, 81MI7; 84MI7; 85MI7; 86MI10).

Pemirolast **3** was introduced into the Japanese market as an orally active antiallergic-asthmatic mediator release inhibitor in 1991 (91MI19, 91MI20; 92MI1, 92MI35). Its antiallergic effects were investigated in different animal models (88MI4, 88MI5; 89MI3, 89MI4; 91MI6; 92MI31) and on human leukocytes and lung fragments (88MI16). The inhibitory effects of pemirolast on release of histamine and leukotriene D<sub>4</sub> and B<sub>4</sub> and on production of platelet-activating factor were also studied (93MI5). The general pharmacology of pemirolast was studied *in vivo* and *in vitro* (89MI26). Its subacute toxicity (89MI29) and its chronic toxicity (89MI21) in dogs were investigated and reported. Perinatal, postnatal, and fertility studies of pemirolast were also reported (90MI10, 90MI12). The mutagenicity of pemirolast was evaluated by using the bacterial reversion and the *in vitro* chromosomal aberration tests (89MI22). Its teratogenicity was studied in rats (90MI11) and in rabbits (90MI13). The metabolic fate of <sup>14</sup>C-pemirolast was investigated in rats (89MI23–89MI25). The pharmacokinetics of pemirolast was studied in dogs (90MI14) and in humans (90MI16). The *in vitro* plasma binding of pemirolast by rat, dog, and human plasma has been shown to be independent of its concentration (90MI18). From dog and human blood and urine samples 9-hydroxymethyl and glucuronyl and glucopyranosyl derivatives **689** and **690** were isolated together with unchanged pemirolast **3** (90MI15, 90MI17). The mechanism of action of pemirolast was also investigated (91MI6; 92MI17, 92MI25, 92MI27). The clinical effectiveness of pemirolast was also reported (91MI7; 92MI2). The preparation of pemirolast antiallergic nasal and eye drops, ointments,



and creams, was reported along with the combination of pemirolast with an antiinflammatory drug in a sustained-release preparation [89EUP316174, 89MIP1; 91JAP(K)91/118323; 92JAP(K)92/300831, 92JAP(K)92/368330]. A toxicological study of pemirolast eye drops in rabbits has been published (90MI8). Bioequivalence between tablets and dry syrup containing pemirolast was investigated in humans (91MI5; 92MI20).

Aerosol formulations (90EUP403301) and nasal and eye drops (91EUP407000) of AS-35 (**4**) have been developed and patented for treating allergic disorders. AS-35 was claimed as a component in a combination containing a PAF antagonist and LTD<sub>4</sub> antagonist (92EUP469477). Antiallergic activities and the pharmacological profile of AS-35 were also investigated (91MI18; 92MI12, 92MI13, 92MI15; 93MI8, 93MI10). Peptide leukotriene antagonistic activities of AS-35 were investigated *in vitro* and *in vivo* (92MI14). Different formulations and application as antiinflammatory agents of AS-35 and its derivatives have also been patented (93MIP9; 94MIP1).

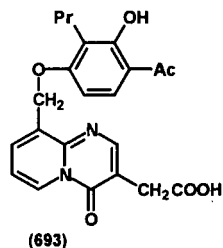
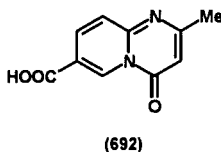
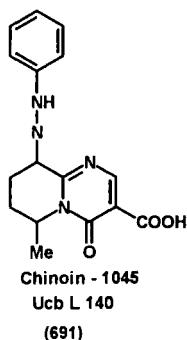
In addition, AS-35 (**4**) has been patented as a remedy for inflammatory intestinal disease (94MIP1) and as an oral antiallergic composition, together with its homologs and 3-carboxylic acid derivatives (93MIP9).

Pretreatment with the antiinflammatory Chinoin-127 (**19**) has been shown to restore the disrupted PGI<sub>2</sub>/TXA<sub>2</sub> balance of gastric mucosa in indometacin-treated rats (89AF686). Chinoin-127 did not exhibit significant opioid agonist activity on different tests (88MI10). The influence of formulation upon resorption of Chinoin-127 from ointments was investigated (84MI1). Its metabolism was investigated in rats and dogs (81MI8).

The effects on immunological reactions of Chinoin-105 (**355**) and Chinoin-127 (**19**) were investigated (86MI14). The gastroprotective effects and mechanism of action of rimazolium (**1**), pemirolast (**3**), Chinoin-105 (**355**) and its *N'*-*tert* butyl derivative, and Chinoin-127 (**19**) were studied in rats (86EUP182569, 86MI26; 87MI9, 87MIP1; 89MI5; 92MI28, 92MI32, 92MI34). The citoprotective activities of *N*-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides have been reported (92MI33), and the structure-activity relationship was also studied.

The bronchospasmolytic activities of 2,3-dialkyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and their tetrahydro derivatives against serotonin, histamine-, and acetylcholine-induced spasms were determined in the guinea pig Konzett–Roessler test (87JMC1543). The metabolism of one of the most active compounds, Chinoin-150 (**347**), was investigated in rats and dogs (81MI8); it was also studied *in vitro* in rat-liver microsomes (89MI13) and the isolated perfused livers of 3-methylcholanthrene- or phenobarbital-treated and untreated rats (90MI2). A prediction of retention of metabolites of Chinoin-150 in HPLC was given by an expert system approach (89MI14). Unchanged Chinoin-150 was determined in rat serum and some organs by GC (81MI6).

Among the antiallergic 9-substituted 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids (82JMC1140; 83JMC1126, 83JMC1494; 84JMC1253), optically active Chinoin-1045 (Ucb L 140) (**691**) was one of the most active derivatives; it was more potent than sodium cromoglycate and was also active orally (82MI10).



The inhibitory activities of acitemat (**2**), Chinoin-105 (**355**), Chinoin-127 (**19**), Chinoin-150 (**347**) and its 6,7,8,9-tetrahydro derivative, and Chinoin-1045 (**691**) were determined on rabbit lung cAMP phosphodiesterase (81MI1). The preparation of oral-retard formulations of rimazolium (**1**), acitemat (**2**), and Chinoin-150 (**347**) was also claimed (82EUP64388).

The pharmacological activity and biochemical profile of pirenperone (**5**, R = H), a pure and selective S<sub>2</sub>-serotonergic antagonist, were investigated on different test systems (82MI3, 82MI5, 82MI7; 83MI4–83MI6, 83MI14–83MI18; 84MI2, 84MI6, 84MI8, 84MI10, 84MI11; 85MI6, 85MI9, 95MI10, 85MI14, 85MI16, 85MI17, 85MI24, 85MI25, 86MI1, 86MI3, 86MI4, 86MI6–86MI9, 86MI12, 86MI16, 86MI17, 86MI20, 86MI22, 85MI25; 87MI3–87MI5, 87MI7, 87MI8, 87MI10, 87MI13; 88MI12; 90MI5, 90MI19; 91MI9–91MI11; 92MI26, 92MI29; 93MI1), and its application as a veterinary medicine was discussed (83MI19). Pirenperone was also used



as a tool for quantitative autoradiographic mapping of serotonin receptors in the rat brain (85MI1, 85MI5, 85MI15, 86MI24) and for evaluating the role of  $S_2$  receptors and serotonin in the regulation of sexual behavior (89MI11, 89MI27; 90MI9; 91MI8). Preparation of wound-healing compositions containing serotonin antagonists (e.g., pirenperone and metrenperone) was claimed (88EUP268309). Pirenperone was also applied in neuroprotective combinations containing an  $S_2$  antagonist and an  $S_{1A}$  antagonist (92GEP4039631).

Bronchodilator activity of metrenperone (**5**,  $R = Me$ ) in cats against serotonin was investigated (83MI8), and its pharmacological activities were studied in different tests (85MI13; 86MI4; 88MI14). The use of metrenperone was claimed (93CAP2051840), and it was reported for treatment of respiratory distress in mammals (93MI14, 93MI15). Metrenperone inhibited the bronchoconstrictive process triggered by the serotonin challenge (93MI24).

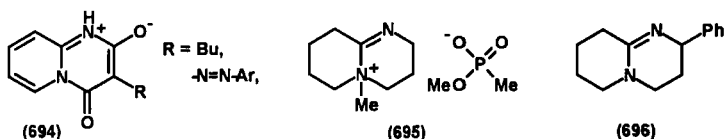
Pharmacological and biochemical properties of the selective serotonin receptor antagonist seganserin (**6**) were studied on different *in vitro* and *in vivo* models (85MI2, 85MI9, 85MI11, 85MI19; 86BJP129, 86MI8, 86MI21; 87MI12; 88MI9, 88MI14; 89MI9). Seganserin was claimed for treating addiction to habit-forming drugs (91EUP461705).

FDA approved the introduction of risperidone (**7**) in 1993 and antipsychotic agent (92MI3; 93MI21). The pharmacological activities and biochemical profile of risperidone were investigated on different *in vitro* and *in vivo* models (88MI9, 88MI11, 88MI13, 88MI15; 89MI1, 89MI8, 89MI12, 89MI20, 89MI28; 90MI3, 90MI4, 90MI7; 91MI12–91MI17; 92JMC552, 92MI4–92MI9, 92MI16, 92MI18, 92MI19, 92MI21, 92MI22; 93MI3, 93MI4, 93MI6, 93MI7, 93MI9, 93MI11–93MI13, 93MI16–93MI18, 93MI21–93MI23, 93MI26; 94MI1). The therapeutic effect of risperidone was also investigated in humans (89MI17, 89MI18; 90MI6; 93MI2). Topical preparations of serotonin antagonists, among them risperidone, were patented (90SAP90/06583; 91MIP1). A PET study was reported using risperidone *in vivo* in humans (93MI2).

The pharmacological profile and amphetamine antagonism of ocaperidone (**8**) were reported on rats (92MI6, 92MI10, 92MI16, 92MI21; 93MI1). Ocaperidone was found to have both  $D_2$ -dopaminergic and  $S_2$ -serotonergic antagonist activities (90MI21–90MI23).

The oral antiallergic activity of ramastatine (**9**) was investigated in ascaris-hypertensive dogs (86MI5). 4*H*-Pyrido[1,2-*a*]pyrimidine-7-carboxylic acid (**692**) was ineffective in inhibiting human leukocyte alkaline phosphatase and rat passive cutaneous anaphylaxis (82JMC742). 4*H*-Pyrido[1,2-*a*]pyrimidine-3-acetic acid (**693**) and its tetrazole analog were patented as agents for the treatment of liver diseases [88JAP(K)88/243082].

The application of "malonyl- $\alpha$ -aminopyridine" (37) was claimed in shampoo as a coupler (81GEP3009833). The 3-butyl derivative of malonyl- $\alpha$ -aminopyridine (694, R = Bu) inhibited senescence of illuminated soybean seedlings under low carbon dioxide conditions, but did not decrease leaf light transmission at ambient carbon dioxide levels (84MI14). 3-Arylazo derivatives of malonyl- $\alpha$ -aminopyridine (694, R = Ar—N=N—) are used as dyestuffs, and the effect of the substituents of the aryl ring on the color of azo dyes was investigated (89MI6).



3(2*H*)-Tellurazolepropanesulfonic acid derivatives of pyrido[1,2-*a*]pyrimidine are used as sensitizers in silver halide photographic photosensitive materials [86JAP(K)86/275744, 86JAP(K)86/277942]. Pyrido[1,2-*a*]pyrimidine derivatives are claimed as dyes for manufacturing silver halide photographic materials [89JAP(K)89/224749]. 3*H*-Indolium and benzothiazolium derivatives of malonyl- $\alpha$ -aminopyridines are used in the manufacture of optical laser recording materials (85USP4551413), and as antihalation and/or acutance dyes in photographic elements (83EUP101646).

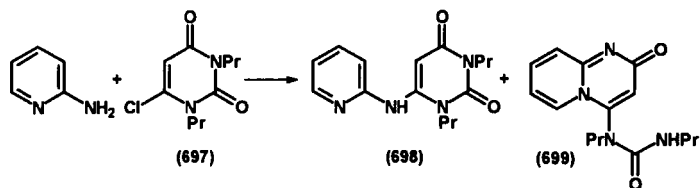
2-Ethylhexanoate salt of 3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine is used as catalyst for crosslinking epoxy resins with hexahydrophthalic anhydride [81JAP(K)81/131620]. 3,4,6,7,8,9-Hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine was patented as curing accelerator for bonding of steel or aluminum plates with two-component polyurethane adhesives [90JAP(K)90/208381]. A salt of 3,4,5,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine with a 1*H*-benzimidazolium hydroxide inner salt is claimed as a photographic spectral sensitizer in multilayered color-photographic photosensitive materials [84EUP115304; 87JAP(K)87/91945; 91JAP(K)91/18841]. 3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine was also claimed as a member of epoxy resin potting compositions [92JAP(K)92/174545]. A quaternary salt of 3,4,5,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine was used in electrophotographic toner [93JAP(K)93/100490].

The methyl methylphosphonate quaternary salt 695 was patented as catalyst in curing of polyisocyanate (85GEP3328662). The 2-phenyl derivative of hexahydropyrido[1,2-*a*]pyrimidine (696) was patented as a catalyst for curing of blocked isocyanate-terminated polycarbonate (87EUP247692). Pyrido[1,2-*a*]pyrimidine-8-nitrile derivatives were

claimed for use in electrophotographic photoreceptors [92JAP(K)92/194863].

## VI. Appendix

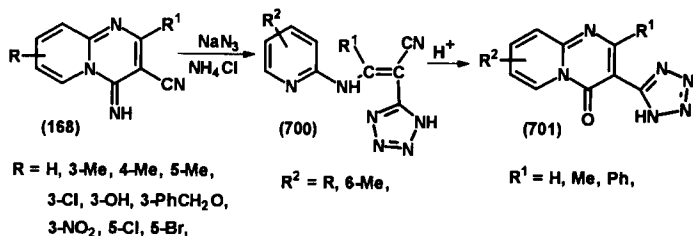
2-Aminopyridine was treated with sodium hydride in tetrahydrofuran at room temperature for 1 hour; then 6-chloro-1,3-dipropylpyrimidinedione **697** was added to the reaction mixture, which was stirred overnight at room temperature (94JHC81). After work-up and chromatography, 6-(2-pyridyl)aminopyrimidinedione **698** and 2*H*-pyrido[1,2-*a*]pyrimidin-2-one **699** were obtained in 34% and 12% yield, respectively. In the case of 2-amino-5-chloropyridine, the appropriate pyrimidinedione was obtained in 62% yield.



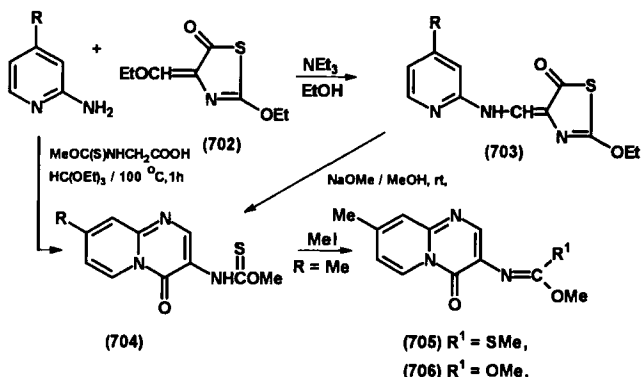
3-Substituted “malonyl- $\alpha$ -aminopyridines” **109** ( $R = 7$ -halogen) were prepared in the reaction of 2-amino-5-halo-2-aminopyridine and diethyl-substituted malonates by heating in diethylbenzene for 1 hour under reflux, or in the absence of a solvent at 175°C for 3 hours (93MIP8). The pyrido[1,2-*a*]pyrimidin-4-ones were alkylated with alkyl or allyl halogenides in dimethylformamide at ambient temperature in the presence of potassium carbonate for 8–15 hours to yield 2-alkoxypyridopyrimidin-4-ones. 2-Chloropyrimidopyrimidin-4-ones were obtained by heating in an excess of phosphoryl chloride for 88 hours. The 2-chloro atom was exchanged by propyl mercaptan by heating in dimethylformamide in the presence of potassium carbonate.

Reaction of 4-imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitriles **168** and sodium azide in the presence of ammonium chloride in dimethylformamide at 80–100°C for 1–3 hours gave 3-(2-pyridylamino)-2-(1*H*-tetrazol-5-yl)acrylonitriles **700** (93MIP6). 3-(2-Pyridylamino)-2-(1*H*-tetrazol-5-yl)acrylonitriles **700** were cyclized to 3-(1*H*-tetrazol-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **701** by heating in concentrated hydrochloric acid under reflux for 1 hour or by heating in polyphosphoric acid at 130–140°C for 2–4 hours (93MIP7).

Reaction of 2-aminopyridines and 2-methoxy-4-ethoxymethylene-



5(4*H*)-thiazolone **702** at ambient temperature for 24 hours gave condensation products **703** in 37–40% yields (94JHC125). A suspension of condensation product **703** ( $\text{R} = \text{Me}$ ) in methanolic sodium methylate was stirred for 24 hours to afford 3-methoxythiocarbonylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **704** ( $\text{R} = \text{Me}$ ). If the methanolic reaction mixture of condensation products **703**, after standing at room temperature for 24 hours, was treated with methyl iodide for 3 hours at room temperature, then 3-amino- and 3-amino-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **412** were obtained in 34–61% yields.

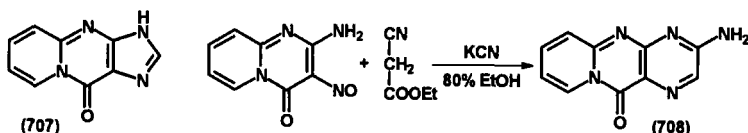


3-Methoxythiocarbonylamino-4*H*-pyridopyrimidin-4-one **704** ( $\text{R} = \text{H}$ ) was obtained in 23% yield when *N*-methoxythiocarbonylglycine and triethyl orthoformate were reacted in acetic acid. The reaction mixture was evaporated *in vacuo* to dryness, the residue was dissolved in ethanol, and triethylamine and 2-aminopyridine were added. Then the reaction mixture was left to stand at room temperature for 1 week (94JHC125). The treatment of 3-methoxythiocarbonyl-8-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **704** ( $\text{R} = \text{Me}$ ) with methyl iodide in methanolic sodium methylate at ambient temperature for 3 hours afforded 3-(1-methylthio-1-methoxymethyleneamino) (**705**) and 3-dimethoxymethyleneamino derivatives (**706**) in 23% and 3% yields, respectively.

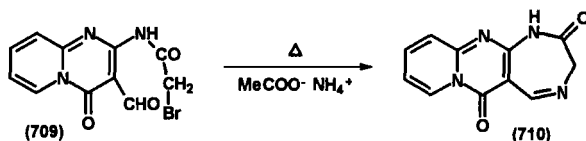
Nitration of 3-unsubstituted 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with a mixture of concentrated sulfuric acid and concentrated nitric acid in the presence of a few drops of acetic anhydride under cooling yielded 3-nitro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [93IJC(B)978].

4*H*-Imidazo[5,4-*d*]pyrido[1,2-*a*]pyrimidin-4-one **707** was obtained in 45% yield when a mixture 2,3-diamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and formamide was heated at 180°C for 30 minutes (92MI23).

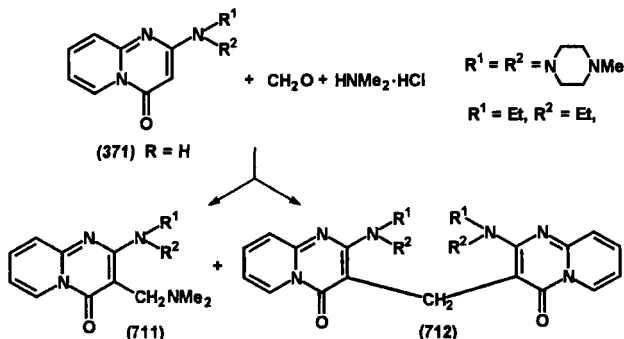
Heating a mixture of 2-amino-3-nitroso-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, potassium cyanide, and ethyl cyanoacetate afforded 2-amino-5*H*-pyrazino[5,6-*e*]pyrido[1,2-*a*]pyrimidin-5-one **708** (92MI23).



Pyrido[1',2':1,2-*a*]pyrido[4,5-*e*]-1,4-diazepine-2,6-dione **710** was obtained in 45% yield when 2-(chloroacetyl-amino)-3-formylpyridopyrimidin-4-one **709** was heated in liquified ammonium acetate at 180°C for 15 minutes (92MI23).



Reaction of 2-(*N,N*-disubstituted amino)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **371** ( $\text{R} = \text{H}$ ) with an excess of paraformaldehyde and dimethylamine hydrochloride in Dowtherm A at 100–105°C for 90 minutes afforded a mixture of the corresponding Mannich base **711** and 3,3'-methylene bis compound **712** in 12–54% yield, respectively (93FES1225).



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# The Chemistry of Heterocyclic Hydrazonoyl Halides

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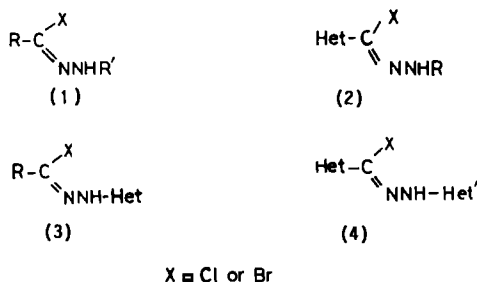
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## I. Introduction

Since their discovery, hydrazonoyl halides **1** have emerged as an important class of intermediates, particularly for the synthesis of heterocyclic compounds. Although several summaries covering the reactions of **1** (where the R and R' groups are alkyl, aryl, alkoxycarbonyl, acyl, arenesulfonyl, or aminocarbonyl) have been published [68MI1; 70CI(L)1216; 80JHC833; 83H2239; 93CRV2731], the chemistry of the heterocyclic hydrazonoyl halides characterized by the structural formulas **2–4** has re-





ceived little attention. The prodigious growth and current research interest in the chemistry of such hydrazoneyl halides within the past ten years prompted us to write this review.

We make no attempt to list the individual hydrazoneyl halides of type 2–4 described in the literature; rather, we shall endeavor to give a broad general review of the synthesis, properties, and reactions of such halides. Furthermore, we sometimes found it necessary to question the mechanisms of some of the reactions and the structures of some of the products outlined herein. The literature was surveyed up to the middle of 1993. The hitherto-reported hydrazoneyl halides of types 2–4 are listed in Table I.

## II. Synthesis

### A. FROM ALDEHYDE HYDRAZONES

Direct halogenation of arylhydrazone derivatives of both aliphatic and aromatic aldehydes with the appropriate halogen in glacial acetic acid is an excellent method for the synthesis of the corresponding hydrazoneyl halides **1** [68MI1; 70CI(L)1216]. This same method has also been used for the synthesis of hydrazoneyl halides of types 2–4. For example, the chlorides **13a** and the bromides **13b** were prepared by halogenation of the corresponding *N*-(5-tetrazolyl)hydrazones **44** [71JCS(C)2769]. Likewise, bromination of the heteroarylhydrazones **45** [67JCS(C)239], **46** [68JCS(C)1711], **47** [71JCS(B)2198], **48** (84CPB4437), and **49** [90-IJC(B)895] yielded the corresponding hydrazoneyl bromides **13c**, **14a**, **14b**, **18**, and **21a**, respectively. Halides **21a** were also obtained by refluxing **49** with *N*-bromosuccinimide in dry carbon tetrachloride [90IJC(B)895].

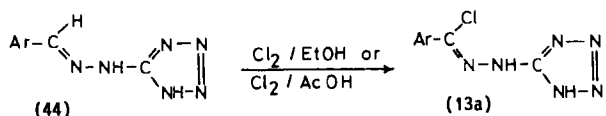
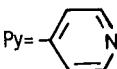
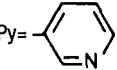
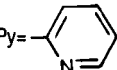
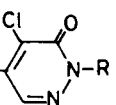

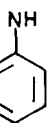

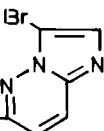



TABLE I

Number	Formula	Substituents
(5)		$R / X / R' / R''$ : (a) $\text{CH}_3 / \text{Cl} / \text{H} / \text{Ph}$ (b) $\text{CH}_3 / \text{Cl} / \text{CH}_3 / \text{Ph}$ (c) $\text{CH}_3 / \text{Cl} / \text{CN} / \text{Ph}$ (d) $\text{CH}_3 / \text{Cl} / \text{Br} / \text{Ph}$ (e) $\text{Ph} / \text{Br} / \text{H} / \text{Ph}$ (f) $\text{EtO} / \text{Cl} / \text{H} / \text{Ph}$ (g) $\text{EtO} / \text{Cl} / \text{NO}_2 / \text{Ph}$ (h) $\text{EtO} / \text{Cl} / \text{Ph} / \text{CH}_3$ (i) $\text{EtO} / \text{Cl} / \text{CN} / \text{Ph}$ (j) $\text{EtO} / \text{Cl} / \text{Br} / \text{Ph}$ (k) $\text{ArNH} / \text{Cl} / \text{H} / \text{Ph}$ (l) $\text{CH}_3 / \text{Cl} / \text{Ph} / \text{CH}_3$
(6)		$R$ : (a) $\text{CH}_3$ ; (b) $\text{EtO}$
(7)		
(8)		$R$ : (a) $\text{CH}_3$ ; b, $\text{EtO}$
(9)		$R / R' / R''$ : (a) $\text{CH}_3 / \text{CH}_3 / \text{COOEt}$ (b) $\text{EtO} / \text{CH}_3 / \text{COOEt}$ (c) $\text{CH}_3 / \text{COOEt} / \text{CH}_3$ (d) $\text{EtO} / \text{COOEt} / \text{CH}_3$ (e) $\text{PhNH} / \text{CH}_3 / \text{COOEt}$
(10)		$R / X / R'$ : (a) $\text{CH}_3\text{CO} / \text{Cl} / \text{H}$ (b) $\text{EtOCO} / \text{Cl} / \text{H}$ (c) $\text{Ar} / \text{Br} / \text{Ph}$ (d) $\text{Ar} / \text{Cl} / \text{Ph}$
(11)		
(12)		
(13)		$X / R$ : (a) $\text{Cl} / \text{H}$ (b) $\text{Br} / \text{H}$ (c) $\text{Br} / \text{CH}_3$ (d) $\text{Br} / \text{Ar}$ (e) $\text{Br} / \text{PhCH}_2$

(continues)

TABLE I (Continued)

Number	Formula	Substituents
(14)	$\text{Ar}-\overset{\text{Br}}{\underset{ }{\text{C}}}=\text{NNH}-\text{C}(\text{N}=\text{N})=\text{N}-\text{N}-\text{R}$	R: (a) CH <sub>3</sub> ; (b) PhCH <sub>2</sub>
(15)	$\text{Py}=\text{Ar}-\overset{\text{Br}}{\underset{ }{\text{C}}}=\text{NNH}-\text{Py}$ 	
(16)		
(17)		
(18)	$\text{Ar}-\overset{\text{Br}}{\underset{ }{\text{C}}}=\text{NNH}-\text{C}(\text{Cl})=\text{N}-\text{N}-\text{R}$ 	
(19)	$\text{Ar}-\overset{\text{X}}{\underset{ }{\text{C}}}=\text{NNHCO}-\text{N}$ 	X: (a) Cl; (b) Br
(20)	$\text{RCO}-\overset{\text{X}}{\underset{ }{\text{C}}}=\text{NNH}-\text{C}(\text{N}=\text{N})=\text{N}-\text{H}$ 	R / X: (a) CH <sub>3</sub> / Cl (b) EtO / Cl (c) Ph / Br
(21)	$\text{RCO}-\overset{\text{X}}{\underset{ }{\text{C}}}=\text{NNH}-\text{C}(\text{N}=\text{N})=\text{N}-\text{H}$ 	R / X: (a) Ar / Br (b) CH <sub>3</sub> / Cl (c) EtO / Cl
(22)	$\text{Ar}-\overset{\text{Br}}{\underset{ }{\text{C}}}=\text{NNH}-\text{C}(\text{Br})=\text{N}-\text{N}-\text{R}$ 	
(23)	$\text{Ar}-\overset{\text{Br}}{\underset{ }{\text{C}}}=\text{NNH}-\text{C}(\text{S})=\text{N}-\text{N}-\text{R}$ 	

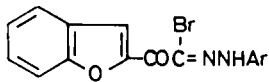
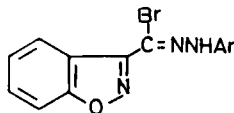
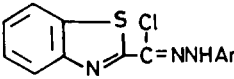
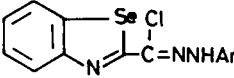
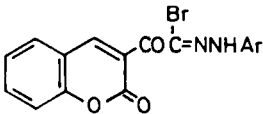
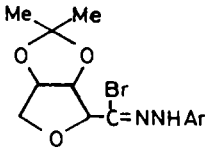
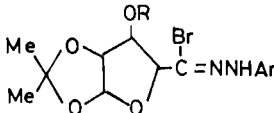
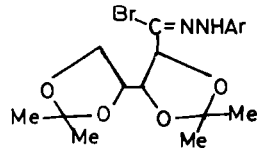
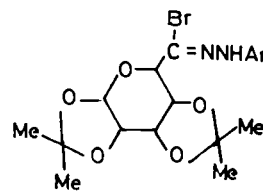
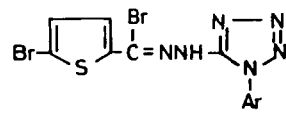
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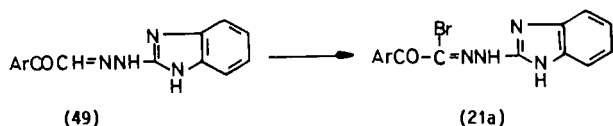
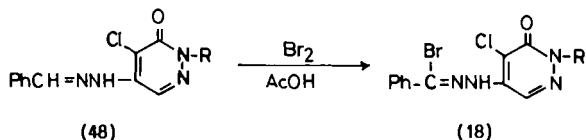
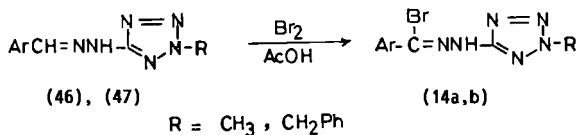
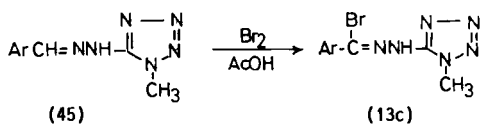
TABLE I (Continued)

Number	Formula	Substituents
(24)		
(25)		
(26)		
(27)		
(28)		R / X: (a) H / Cl (b) H / Br (c) Br / Br
(29)		
(30)		R / R' / R'': (a) H / H / CONH <sub>2</sub> (b) H / H / CONHCH <sub>3</sub> (c) Br / CH <sub>3</sub> / CONHCH <sub>3</sub> (d) H / H / CON(CH <sub>3</sub> ) <sub>2</sub> (e) H / H / Ar
(31)		
(32)		
(33)		

(continues)

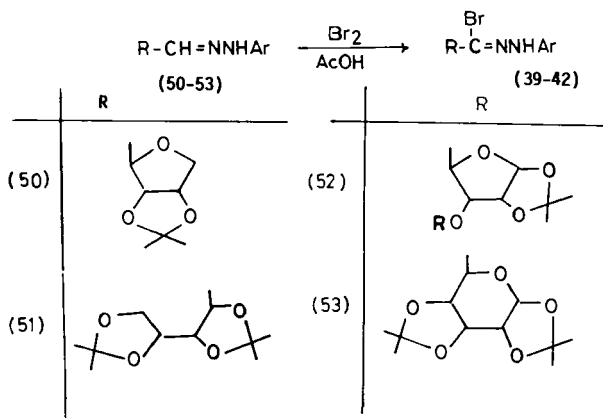
TABLE I (Continued)

Number	Formula	Substituents
(34)		
(35)		
(36)		
(37)		
(38)		
(39)		
(40)		R: (a) CH <sub>3</sub> ; (b) PhCH <sub>2</sub>
(41)		
(42)		
(43)		



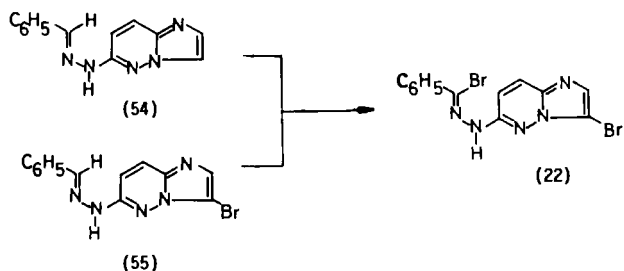
(46), R = CH<sub>3</sub>; (47), R = PhCH<sub>2</sub>

Bromination of the *p*-nitrophenylhydrazones **50–53** yielded the corresponding hydrazoneyl bromides **39–42**, respectively (71HCA921; 74MI1, 74MI2).

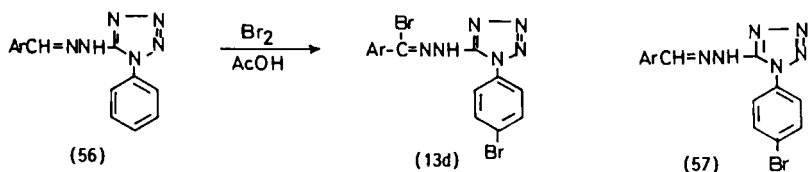


Ar = 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>

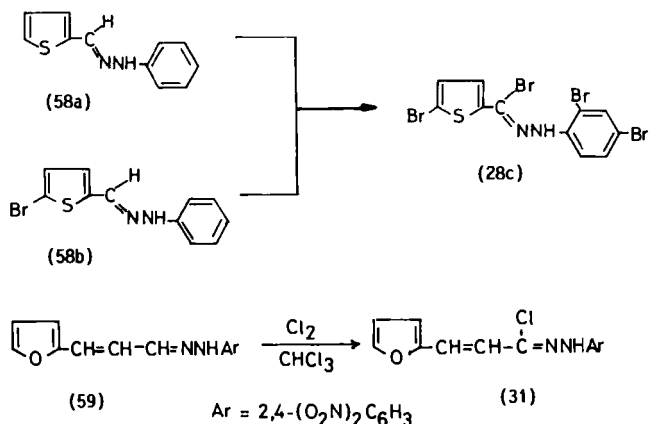
Sometimes, halogenation of the *N*-heteroaryl moiety cannot be avoided under such reaction conditions. For example, bromination of hydrazone **54** or **55** afforded the hydrazonoyl bromide **22** (67T387). Also, reaction of bromine with *N*-(5-tetrazolyl)hydrazones **56** under similar conditions gave two products identified as **13d** and **57** (91MI2).



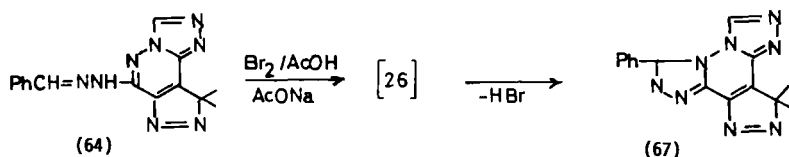
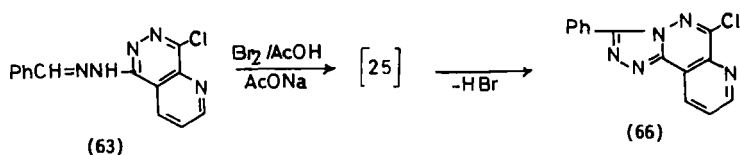
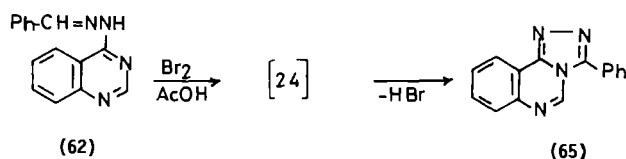
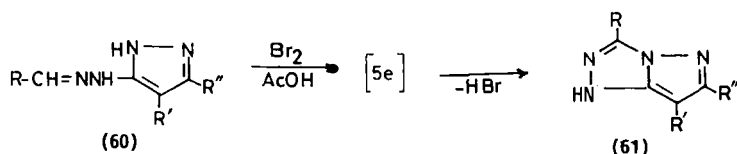
Furthermore, direct halogenation sometimes leads to substitution in the *C*-residue of the aldehyde hydrazone. For example, hydrazonoyl bromide **28c** was obtained by direct bromination of hydrazone **58a** or **58b** (75CJC1484). Electron-withdrawing substituents in the *N*-aryl moiety of the arylhydrazone derivatives of heterocyclic aldehydes inhibit ring bromi-



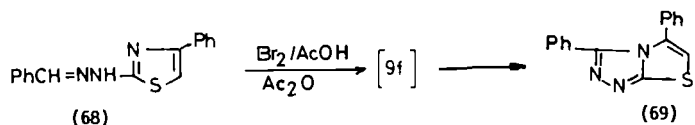
nation. Thus, chlorination of **59** with chlorine in chloroform at room temperature yielded hydrazonoyl chloride **31** (81MI1).



Bromination of aldehyde *N*-heteroarylhydrazones in acetic acid in the presence of sodium acetate sometimes leads to intramolecular cyclization of the initial hydrazoneyl bromides to yield the corresponding cyclized products. For example, bromination of *N*-(5-pyrazolyl)hydrazones **60** under such conditions afforded pyrazolo[5,1-*c*][1,2,4]triazoles **61**, presumably via the hydrazoneyl bromides **5** (70FRP2075583, 70GEP1810463). Similar treatment of the *N*-heteroarylhydrazones **62** (63T1587), **63** (67JOC1139), and **64** (86S78) afforded the cyclized products **65–67**, respectively.

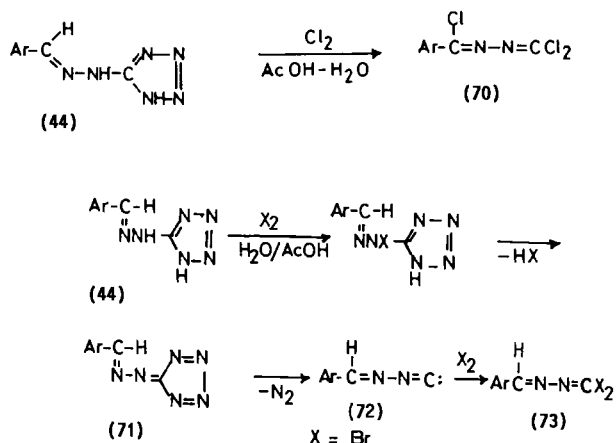


Sometimes, the intramolecular cyclization of the intermediate hydrazoneyl halides occurs even in the absence of sodium acetate. Thiazolo[2,3-*c*]triazole **69** was the sole product isolated from direct bromination of hydrazone **68** (90MI2).





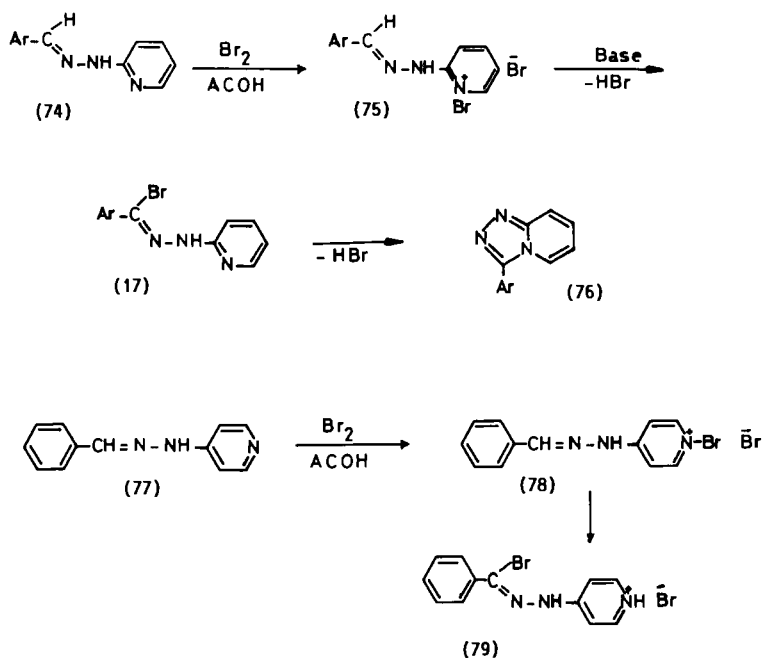
Direct halogenation of *N*-(5-tetrazolyl)hydrazones in aqueous acetic acid can lead to the cleavage of the heteroaryl moiety. For example, chlorination of *N*-(5-tetrazolyl)hydrazones **44** gave 1,1,4-trichloro-2,3-diazabutadienes **70** in 65–75% yields [70TL4079; 72JCS(P1)2214]. Also, bromination of **44** under similar conditions gave the dibromoazine **73** [64CI(L)1757; 70TL4079; 72JCS(P1)2214, 72JCS(P2)1050]. This reaction involves initial *N*-bromination and loss of hydrogen bromide to give a tetrazol-5-ylidene hydrazine **71**, followed by production of the isocyanide **72** which adds bromine to yield the dibromide **73** (70TL4079).



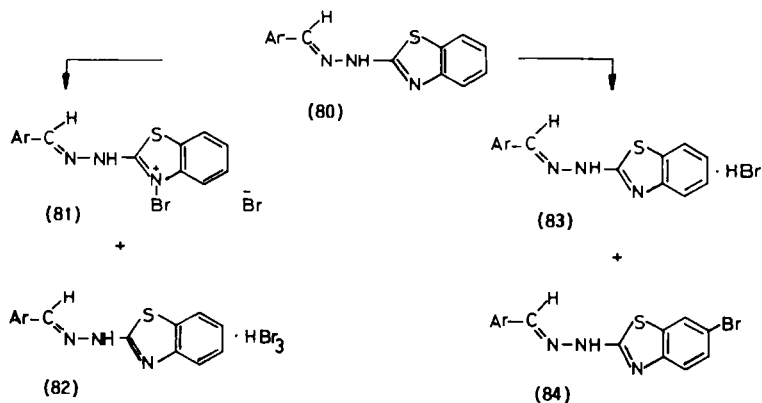
Sometimes bromination of *N*-heteroarylhydrazones gave 1 : 1 addition products first. For example, bromination of 2-pyridylhydrazones **74** produced the 1 : 1 adduct **75**. Treatment of the latter with a base afforded 3-phenyl-*s*-triazolo[4,3-*a*]pyridines **76**, presumably via intramolecular cyclization of the corresponding hydrazoneoyl bromides **17** (63T1587). Similar treatment of 4-pyridylhydrazone **77** also gave the 1 : 1 addition complex **78** which afforded, however, the hydrazoneoyl bromide hydrobromide **79** on refluxing in acetone [73JCS(P2)1466].

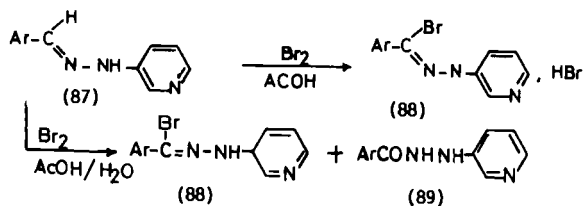
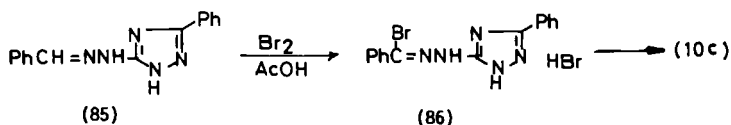
Likewise, bromination of the benzothiazolylhydrazone **80** for a short period in glacial acetic acid yielded molecular complexes **81** and **82** when the starting hydrazones had electron-withdrawing and electron-donating substituents, respectively [72JCS(P1)1519]. However, by varying the conditions, low yields of the hydrazoneoyl bromides **23** (9–37%) were isolated together with the hydrobromides **83** (48–62%) and 6-bromobenzothiazol-2-ylhydrazones **84** (4–9%) [72JCS(P1)1519].

Bromination of hydrazone **85** gave hydrobromide **86** which, upon distribution between ether and water, afforded the hydrazoneoyl bro-

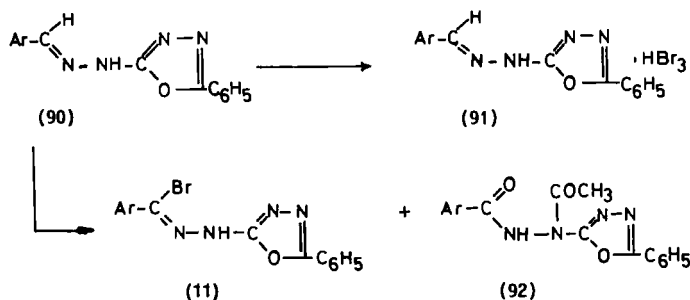


mide **10c** [65TL841; 74JCS(P2)997]. Also, direct bromination of *N*-(3-pyridyl)hydrazones **87** gave the hydrobromide **88** in good yields [72JCS(P2)1892]. However, bromination of **87** in 70% acetic acid yielded a mixture of salt **88** and hydrazide **89**. Hydrazide **89** is the expected hydrolysis product of **16** [71JCS(B)1607; 72JCS(P2)1892].

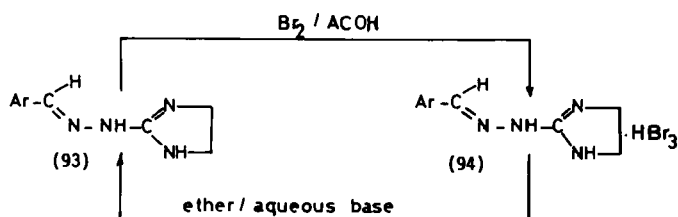




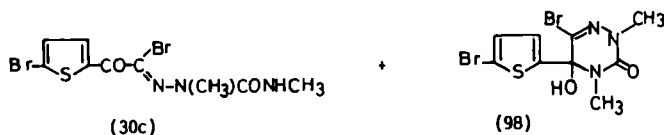
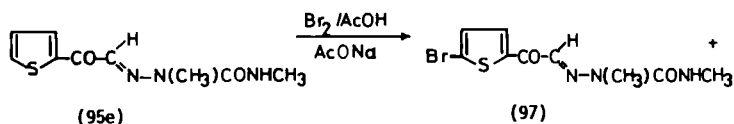
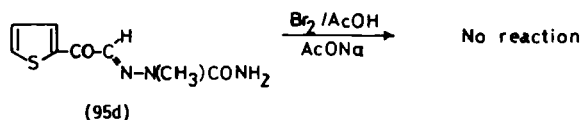
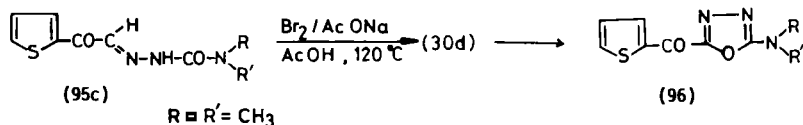
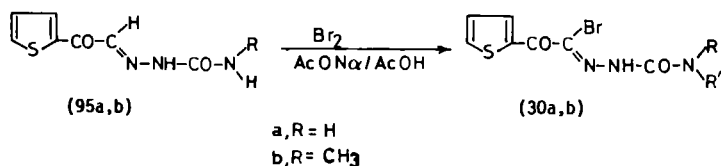
Occasionally, bromination of *N*-heteroarylhydrazones in acetic acid with an excess of bromine yielded the hydrazone perbromide. For example, with 2 mole equivalents of bromine, hydrazone **90** afforded perbromides **91**, whereas bromination of **90** with 1 mole equivalent of bromine in the presence of sodium acetate gave a mixture of the hydrazone bromide **11** and *N*-acetylhydrazone **92** [72JCS(P1)269]. By-product **92** arose from the reaction of **11** with acetate ion, a reaction typical of hydrazone bromides [63AG(E)565, 63AG(E)633]. Hydrazone perbromide **94** was also obtained on bromination of hydrazone **93**. It reverted to the starting hydrazone **93** upon distribution between ether and aqueous base (70TL4083).



Bromination of 2-(2-thienyl)glyoxal-1-*N*-carbamoyl hydrazones **95** in glacial acetic acid in the presence of sodium acetate produces products that depend upon the type of substitution on the hydrazone moiety and on the experimental conditions. For example, bromination of **95a,b** at room temperature gave the hydrazone bromides **30a,b**, respectively. Similar treatment of **95c** at either 120°C or 25°C afforded the oxadiazole **96** via cyclization of the intermediate hydrazone bromide **30d**. On the

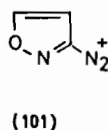
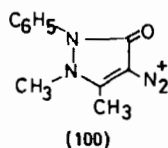
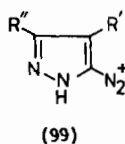


other hand, compound **95d** was recovered unchanged upon similar treatment, whereas bromination of **95e** afforded a mixture of three products, namely **30c**, **97**, and **98** (78JHC1393).

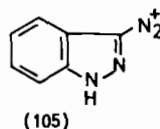
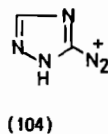
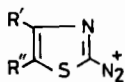


## B. FROM ACTIVE CHLOROMETHYLENE COMPOUNDS

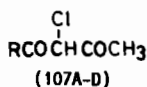
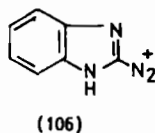
The coupling of diazonium salts with a suitably activated chloromethylene group is an excellent method to synthesize hydrazoneyl chlorides of both types 2 and 3. For example, coupling of diazonium salts **99** (77JHC227; 80JHC209; 81M245; 85JHC453; 87AP850; 89MI1; 92MI1), **100** (83AP105), **101** (82MI1), **102** (87MI2; 90MI2; 91MI3), **103** (83JHC285), **104** [82JCS(P1)989], **105** (80JHC209), and **106** (87MI1) each with 3-chloro-2,4-pentanedione, ethyl 2-chloroacetoacetate, and 2-chloroacetoacetanilide **107A-C**, respectively, in aqueous ethanol in the presence of sodium acetate afforded the corresponding *C*-acetyl-, *C*-ethoxycarbonyl-, and *C*-arylaminoacetyl-*N*-heteroarylmethanehydrazoneyl chlorides **5**, **6**, **8**, **9**, **10**, **20** and **21** (Table I).



R' / R'' : a, Ph / H; b, CH<sub>3</sub> / Ph;  
c, Ph / NO<sub>2</sub>; d, Ph / Br  
e, Ph / CN

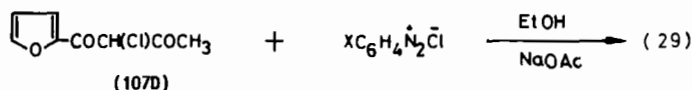


R' / R'' : (102) CH<sub>3</sub> / COOEt  
(103) COOEt / CH<sub>3</sub>

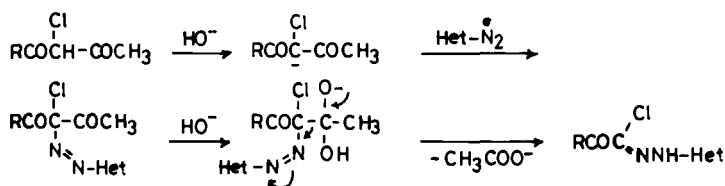


R: A, CH<sub>3</sub>  
B, C<sub>2</sub>H<sub>5</sub>O  
C, XC<sub>6</sub>H<sub>4</sub>NH  
D, 2-Furyl

Similar coupling of diazotized anilines with 2-chloro-1-(2-furyl)-1,3-butanedione **107D** under similar conditions gave the 2-(2-furyl)-2-oxo-*N*-arylethanehydrazoneyl chlorides **29** (82H57).

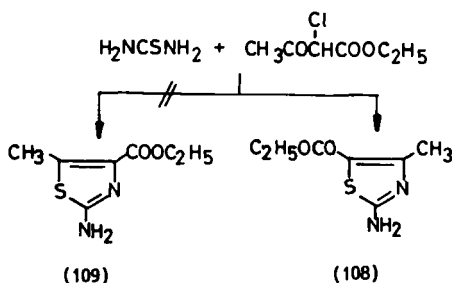


The foregoing reactions follow the mechanism proposed for the Japp-Klingmann reaction as outlined in Scheme 1 (59OR143).



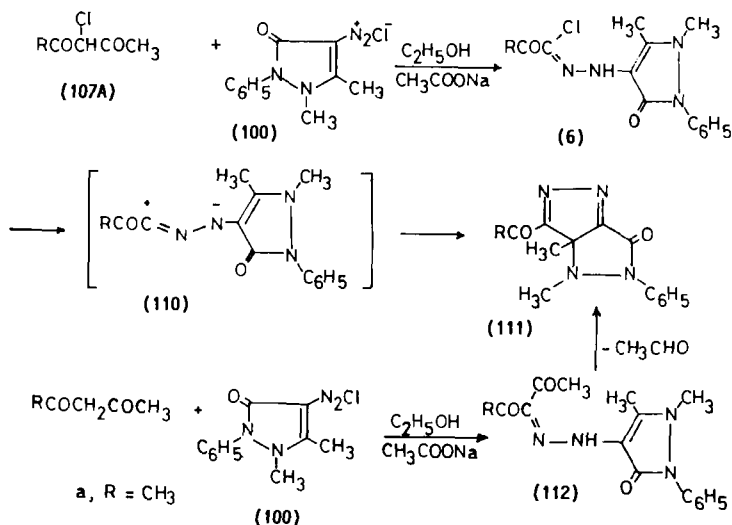
SCHEME 1

It should be pointed out that the two apparently isomeric hydrazoneyl chlorides **9a** (87MI1) and **9c** (83JHC285) represent one and the same compound, namely **9a**. Both compounds **9a** and **9c** were prepared by coupling a diazotized 2-thiazolamine derivative, prepared by a cyclization reaction of thiourea with ethyl  $\alpha$ -chloroacetoacetate (1893LA79). The cyclized product should have structure **108** and not the erroneously assigned structure **109** (83JHC285). The identity of both **9a** and **9c** is confirmed by the fact that both have the same melting point (145°C). Also, based on the same argument, the two isomeric hydrazoneyl chlorides **9b** (87MI2) and **9d** (83JHC285) correspond to one compound, namely **9b**, as they were prepared from the same starting materials and their reported melting points are also similar (149° and 150°C).

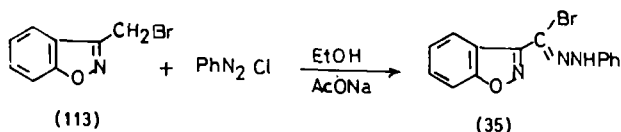


Sometimes the hydrazoneyl chlorides prepared by this method undergo *in situ* cyclization. For example, attempted coupling of diazotized 4-amino-1,5-dimethyl-2-phenylpyrazol-3(2*H*)-one **100** with 3-chloro-2,4-pentanedione **107A** afforded pyrazolo[4,3-*c*]pyrazole **111** [82JCS(P1)989]. The formation of **111** can be considered to result from the elimination of hydrogen chloride from hydrazoneyl chloride **6**, followed by cyclization of the resulting nitrilimine **110** (see Section V,A); but it was argued that chloride **6** is not an intermediate in this reaction because coupling of **100** with pentane-2,4-dione also yielded **111** [89ZN(B)951]. On this basis the

authors concluded that coupling of 3-chloro-2,4-pentanedione **107A**, contrary to the literature on the Japp-Klingmann reaction (59OR143), proceeds via elimination of the chloro group to give **112**, which then cyclizes via elimination of acetaldehyde to give **111** [89ZN(B)951].

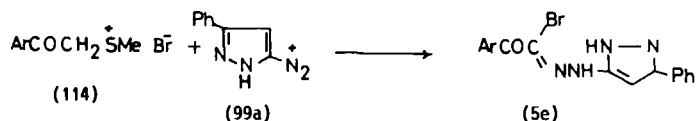


Reactions of benzenediazonium chloride with 3-bromomethylbenzo-[*d*]isoxazole **113** in ethanol in the presence of sodium acetate afforded the hydrazonoyl bromides **35** [90ZN(B)1067].



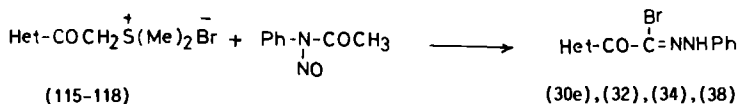
### C. FROM ACTIVE METHYLENESULFONIUM BROMIDES

Reaction of phenacyldimethylsulfonium bromides **114** with diazotized heterocyclic amine **99a** yielded *N*-heteroaryl-2-oxo-2-arylethanehydrazonoyl bromides **5e** (87JHC1341).



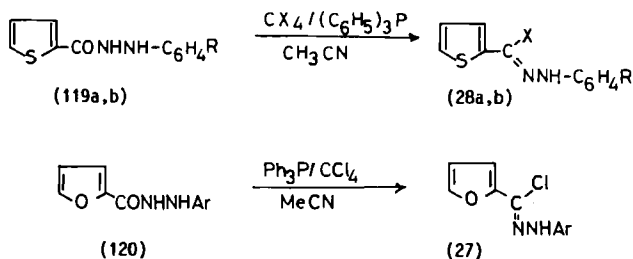
Similarly, *N*-aryl-2-oxo-2-heteroarylethanehydrazonoyl bromides **30e**, **32**, **34**, and **38** were obtained by coupling of the corresponding sulfonium

bromides **115–118**, respectively, with *N*-nitrosoacetarlamides in non-aqueous solvents [88PS(39)45] or with diazotized anilines in ethanol in the presence of sodium acetate (90MI3; 91H1101; 93MI1).



#### D. FROM CARBOXYLIC ACID HYDRAZIDES

The method of Wolkoff (75CJC1333) for transforming *N*-benzoyl-*N'*-arylhydrazines into the corresponding hydrazoneyl halides by the use of triphenylphosphine–carbon tetrahalide ( $\text{Ph}_3\text{P}-\text{CX}_4$ ) has been extended by Shawali *et al.* for the synthesis of heteroarylmethanehydrazoneyl halides. For example, the hydrazoneyl chlorides **28a** (87JHC1665; 88H695) and the hydrazoneyl bromides **28b** (88H695) were prepared by the addition of carbon tetrachloride and carbon tetrabromide, respectively, to a stirred suspension of 1-aryl-2-(2-thenyl)hydrazines **119a,b** and triphenylphosphine in acetonitrile. Similar, treatment of 1-aryl-2-(2-furoyl)hydrazines **120** yielded *N*-aryl-2-furylmethanehydrazoneyl chlorides **27** (90MI1).



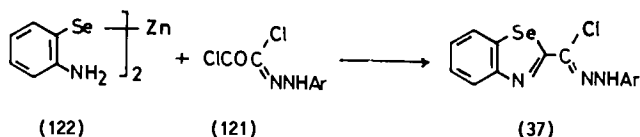
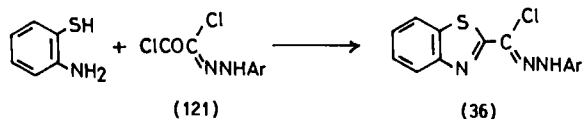
#### E. FROM OTHER HYDRAZONOYL HALIDES

Hydrazoneyl halides having a reactive side-chain functional group other than the halohydrazone group have been used in the synthesis of other hydrazoneyl halides. For example, reaction of *N*-aryl-2-chloro-2-oxoethanehydrazoneyl chlorides **121** with *o*-aminothiophenol afforded hydrazoneyl chlorides **36** (65ZOR1793). A similar reaction of **121** with the zinc salt of *o*-aminobenzeneselenenol **122** gave *N*-aryl-2-benzoselenazolylmethanehydrazoneyl chlorides **37** (65ZOR1793).

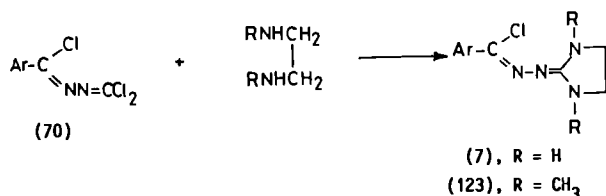
Reaction of trichloro-2,3-diazabutadienes **70** with ethylenediamine and its *N,N'*-dimethyl derivative in benzene gave the corresponding *N*-(2-



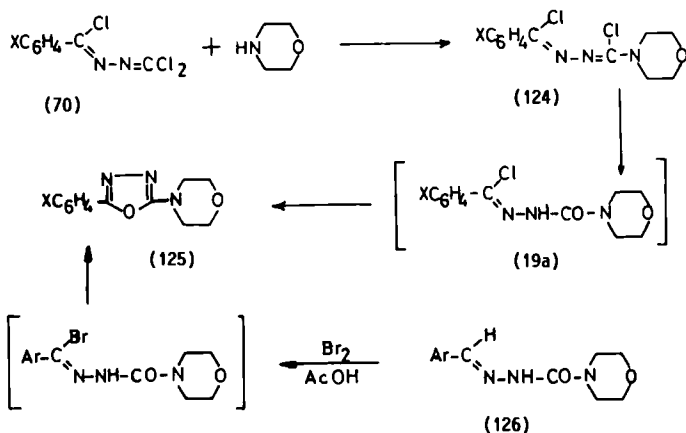
imidazoliny)benzenecarbohydrazonoyl chlorides **7** and **123**, respectively, in good yields [70TL4083; 72JCS(P2)1887].



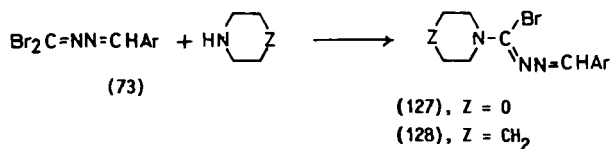
Reaction of **70** with morpholine gave hydrazonoyl chlorides **124** in good yield. When halides **124** were refluxed in 80% aqueous dioxane, they yielded the oxadiazoles **125**, presumably via cyclization of the intermediate



hydrazonoyl chloride **19a** [70T4079; 72JCS(P1)2219]. The intermediacy of **19a** was substantiated by the fact that bromination of the semicarbazones **126** gave the oxadiazoles **125** (69TL4615; 70T4079).



Scott *et al.* (69TL4615) also found that reaction of isocyanogen dibromides **73** with morpholine or piperidine gave the aminohydrazonoyl bromides **127** and **128**, respectively.



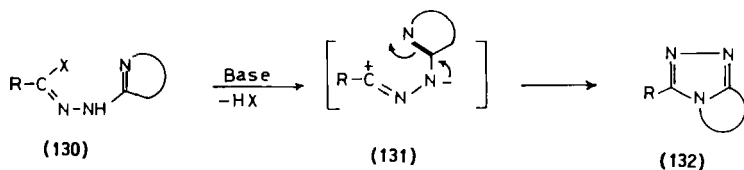
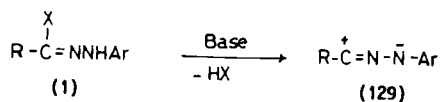
### III. Molecular Spectra

All heterocyclic hydrazonoyl halides **2–4** are crystalline solids. The characteristic IR spectral feature of such hydrazonoyl halides is their NH absorption band. This band appears in the region 3300–3280 cm<sup>-1</sup> for those halides that exhibit no intramolecular hydrogen bonding (87JHC1665; 88H695; 90MI1; 91MI2). C-Acyl and C-alkoxycarbonyl hydrazonoyl halides exhibit an NH band at lower frequencies, 3150–3200 cm<sup>-1</sup> (77HCA2171, 77JHC227; 80JHC209; 81M245; 87AP850; 92MI1). Most hydrazonoyl halides exhibit also a C=N band near 1610 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectra of the hydrazonoyl halides in question reveal the NH proton signal in the region δ 8.2–11.0 ppm as a broad singlet (80JHC209; 81M245; 87AP850, 87MI2; 88H695; 91MI2, 91MI3).

### IV. Reactivity

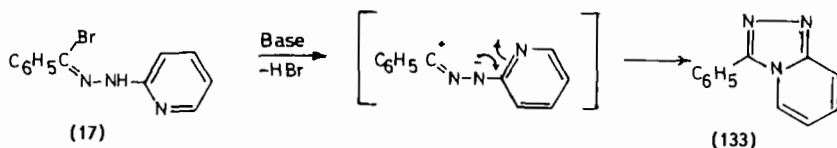
#### A. 1,5-DIPOLAR CYCLIZATION

Base-catalyzed 1,3-elimination of hydrogen halide from hydrazonoyl halides **1** is a well known procedure for the generation of the corresponding nitrilimines **129**. When the *N*-terminal of the resulting nitrilimine is bonded

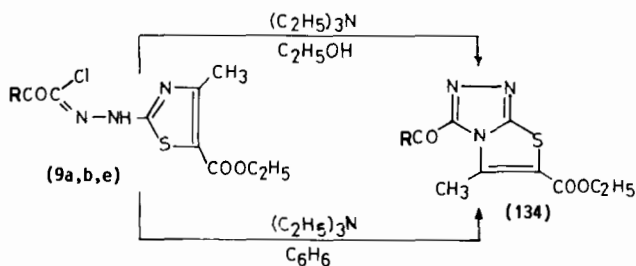


directly to a heterocyclic imino moiety as in **131**, 1,5-dipolar cyclization occurs to give the corresponding fused heterocyclic system **132**. This process is analogous to the electrocyclization of the pentadienyl anion to the cyclopentenyl anion (79CRV181) and is classified by Huisgen as a cycloaddition [68AG(E)312].

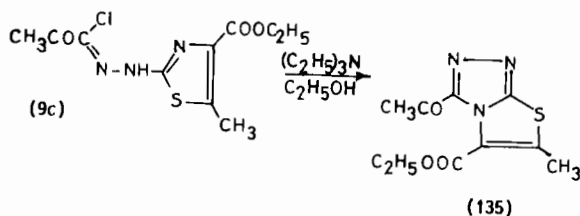
Treatment of *N*-(2-pyridyl)benzenecarbohydrazonoyl bromide **17** with a base affords 3-phenylpyridino[2,1-*c*]-1,2,4-triazole **133** (63T1587).



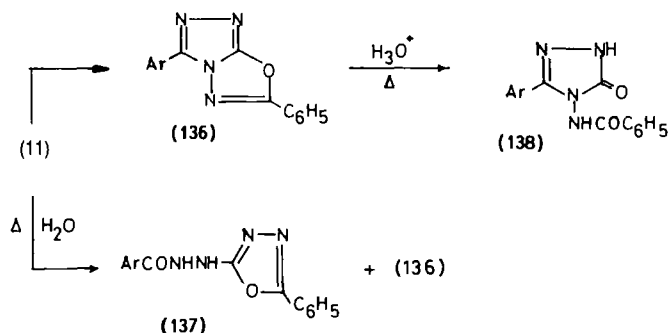
The base-induced 1,3-elimination of hydrogen chloride from *C*-acetyl **9a** [88PS(36)129], *C*-ethoxycarbonyl **9b** [88PS(36)129; 89MI1] and *C*-phenylcarbamoyl **9c** (91MI3) *N*-(2-thiazolyl)hydrazonoyl chlorides afforded the corresponding thiazolo[2,3-*c*]-1,2,4-triazole derivatives **134a-c**, respectively. To the present authors, the other thiazolotriazole derivative **135**, thought to be formed via cyclization of the halide **9c**, should be assigned structure **134a** rather than **135** as reported (83JHC285), because **9c** (as pointed out in Section II,B) is itself **9a**. Furthermore, the melting points reported for **134a** [88PS(36)129] and **135** (83JHC285) are the same, that is, 282°C (EtOH).



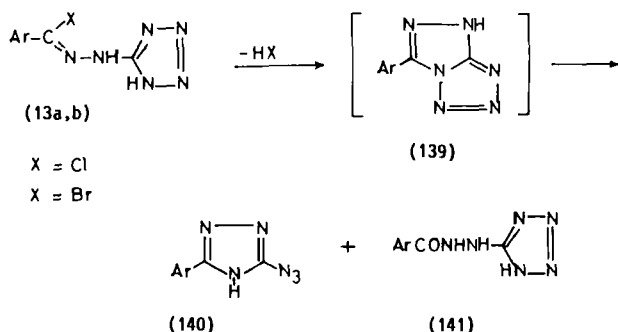
R: a, CH<sub>3</sub>; b, EtO; c, PhNH



1,2,4-Triazolo[3,4-*b*]oxadiazoles **136** were obtained in yields greater than 95% when *N*-2-(5-phenyl-1,3,4-oxadiazolyl)benzohydrazonoyl bromides **11** were heated in benzene under reflux with triethylamine [72JCS(P1)269]. Hydrolysis of **11** also gave **136** but in lower yield (*ca.* 60%) in addition to the aroylhydrazines **137** in 20–40% yields [72-JCS(P1)269]. When refluxed briefly in acetic acid, product **136** undergoes ring cleavage to give the benzamidotriazolones **138** in yields greater than 80%. The same products **138** were also obtained by acid hydrolysis of the bromides **11** [72JCS(P1)269].

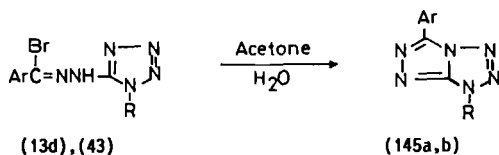
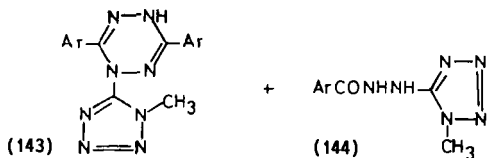
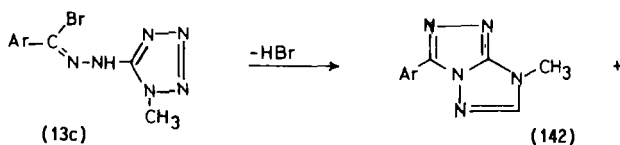


*N*-(5-Tetrazolyl)hydrazonoyl bromides **13a,b** in aqueous ethanol gave 5-azido-3-aryl-1,2,4-triazoles **140** directly without isolation of the intermediate triazolotetrazoles **139** [62MI1; 63TL715]. In some cases hydrazides **141** were produced as by-products [57JOC692; 71JCS(C)2769]. It was suggested that the azides **140** were produced via ring cleavage of triazolo-tetrazoles **139**, which are formed as intermediates.

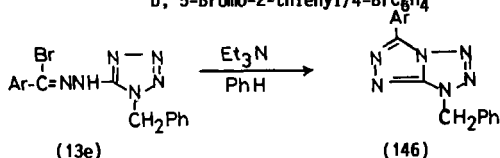


Hydrolysis of *N*-5-(1-alkyltetrazolyl)benzohydrazonoyl bromides **13c** at room temperature in 50% (v/v) acetone–water or dioxane–water mixture in the presence of sodium acetate yielded three products, namely **142–144**,

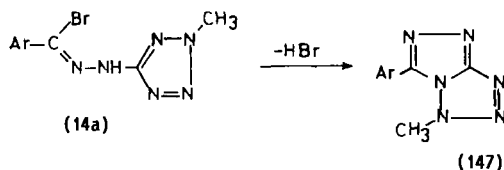
in addition to arenoic acid which resulted from hydrolysis of **144** [67JCS(C)239]. However, solvolysis of **13c** in 90% (v/v) dioxane–water afforded **142** and **143** and 4.5% of arenoic acid [67JCS(C)239]. On the other hand, hydrolysis of *N*-tetrazolyldiazonoyl bromides **13d** and **43** gave only 1,3-dipolar cyclization products **145a** and **145b**, respectively (65AG963; 91MI2). Also, quantitative yields of **146** were obtained by the base-induced 1,3-elimination of hydrogen bromide from **13e** in aprotic solvent [71JCS(B)2198].



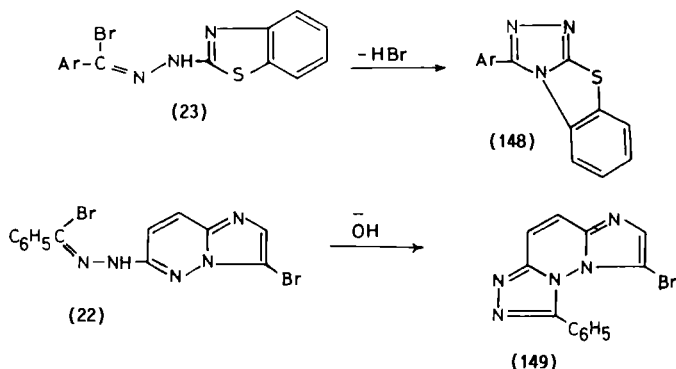
R/Ar: a,  $\text{XC}_6\text{H}_4$ /  $\text{XC}_6\text{H}_4$   
 b, 5-Bromo-2-thienyl/4- $\text{BrC}_6\text{H}_4$



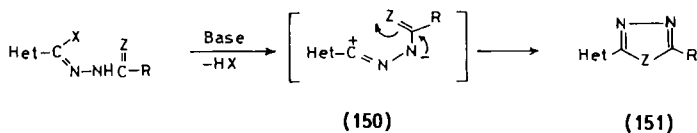
Similar hydrolysis of *N*-5-(2-methyltetrazolyl)benzohydrazonoyl bromides **14a** in aqueous acetone (50% v/v) afforded 1,2,4-triazolo[4,3-*d*]tetrazole **147** in 73% yield [68JCS(C)1711].



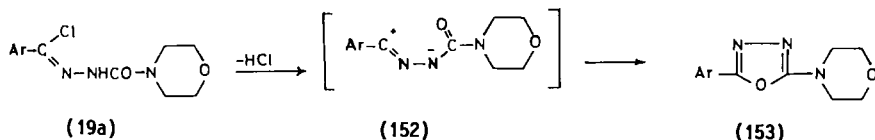
In the presence of base, *N*-(2-benzothiazolyl)benzohydrazonoyl bromides **23** [72JCS(P1)1519] suffer elimination of hydrogen bromide to yield benzothiazolo[2,3-*c*]-1,2,4-triazole derivatives **148**. Also, the action of base on the hydrazonoyl bromides **22** caused their conversion to 1-phenyl-8-bromoimidazo[1,2-*b*]-*s*-triazolo[3,4-*f*]pyridazine **149** (67T387).



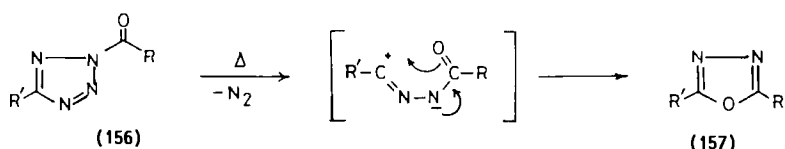
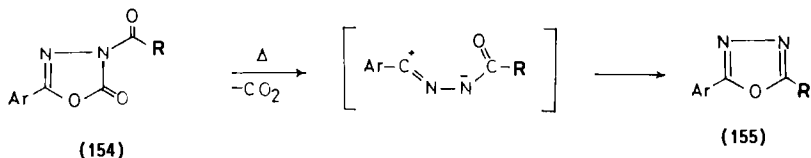
Nitrilimines **150** derived from *C*-heteroarylhydrazonoyl halides having a carbonyl, imino, or thiocarbonyl group attached directly to the *N*-terminal can also undergo 1,5-dipolar cyclization to give the corresponding 1,3,4-oxadiazoles, 1,2,4-triazoles, and 1,3,4-thiadiazoles **151a-c**, respectively. Thus, hydrolysis of the hydrazonoyl chloride **19a** in 80% aqueous dioxane afforded the oxadiazoles **153** (70T4079). The reaction most likely proceeds via carbonylnitrilimine **152**. This synthesis of the oxadiazole ring system is analogous to that involving the 1,5-electrocyclization of the carbonylnitrilimines derived from thermal elimination of carbon dioxide from 4-acyloxadiazol-5-one **154** (13CB4076; 74TL3875). Also, it is similar to that involving the thermal elimination of nitrogen from *N*-acyltetrazoles



Z: (a)O; (b)NH; (c)S



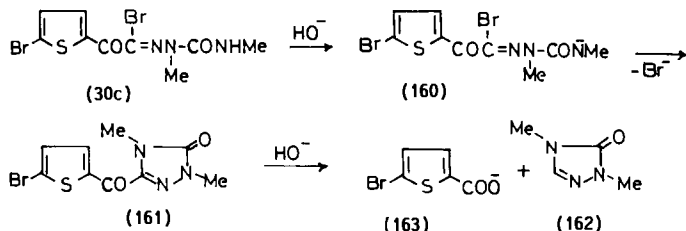
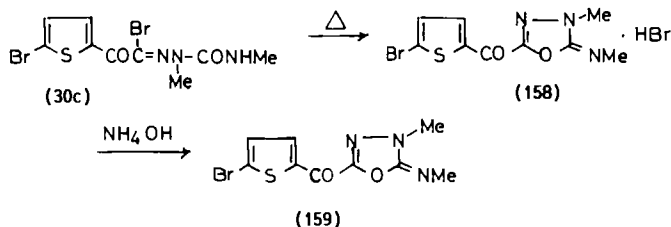
**156** to yield the corresponding 1,3,4-oxadiazoles **157** (60CB2106; 61CB1555). This latter reaction was shown to be broadly applicable in the preparation of alkyl-, aryl-, or aralkyl-1,3,4-oxadiazoles.



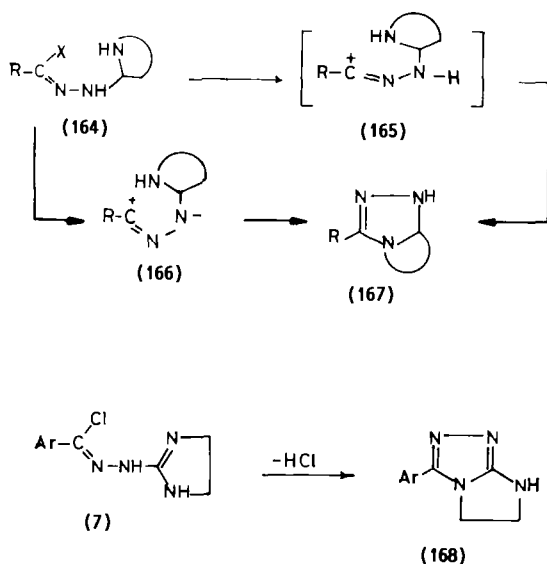
R' = alkyl or aryl

R = alkyl, aryl, alkoxy or ArNH

Heating bromide **30c** in the absence of solvent gave oxadiazoline hydrobromide **158**, which yielded, after basification, the free base **159**. However, treatment of **30c** with sodium hydroxide solution at room temperature or at reflux furnished a mixture of the triazolone derivative **162** (75% yield) and 5-bromothenoic acid **163**, presumably via intramolecular displacement of the bromine atom to give **161**, followed by alkaline cleavage of the thenoyl group (78JHC1393).



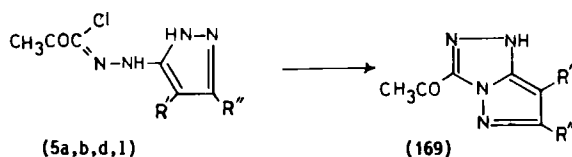
*N*-Heteroarylhydrazonoyl halides **164** having an NH group at the  $\alpha$ -position to the *N*-terminal undergo cyclization to give the corresponding bicyclic derivatives **167**. Such a process can be completed through either intramolecular nucleophilic attack at an azocarbonium-ion intermediate **165** or intramolecular 1,3-dipolar addition to the nitrilimine intermediate **166**. Thus, solvolysis of the hydrazonoyl chlorides **7** in a dioxane-water (4:1) mixture yielded the corresponding 6,7-dihydro-3-aryl-5*H*-imidazolo[2,1-*c*]-*s*-triazoles **168** in good yield. The rate data were correlated by a Hammett equation with  $\rho = -2.9$ . This value is consistent with a mechanism involving an azocarbonium ion of type **165** [70TL4083; 72JCS(P2)1887; 78ZN(B)216].



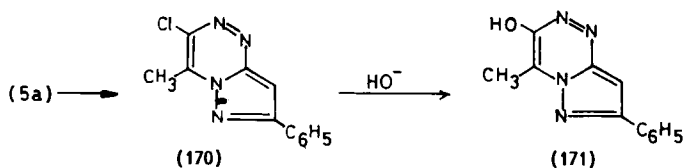
The products obtained from the treatment of *C*-acetyl-*N*-(3-phenyl-4-*R*-5-pyrazolyl)methanehydrazonoyl halides **5a, b, d, l** with triethylamine in benzene or ethanol are the pyrazolo[1,5-*c*]-1,2,4-triazoles **169a-d**, respectively (77JHC227; 80JHC209; 92MI1). However, treatment of **5a** with sodium acetate in ethanol yielded 6-chloro-7-methyl-2-phenylpyrazolo[5,1-*c*]-1,2,4-triazine **170**. Solvolysis of **170** in aqueous sodium hydroxide gave **171**. Attempted cyclization of **5a** with methylamine or hydrazine hydrate in methanol gave **171** directly (77JHC227).

Different cyclization products were also obtained from ethanolysis of **51** according to the reaction conditions. Thus, in the absence of a base the pyrazolotriazine **172** was produced (81M245), whereas in the pres-

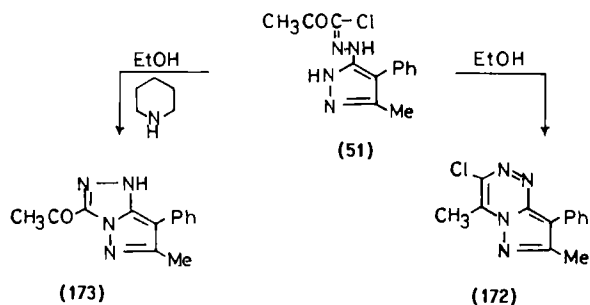




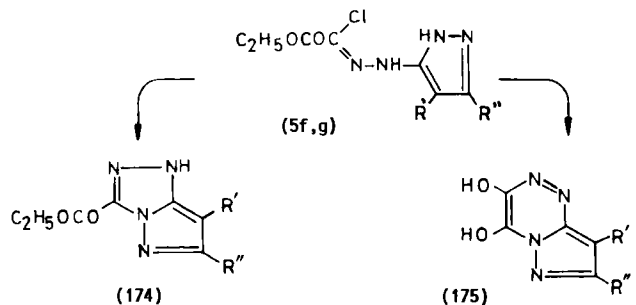
$R'/R''$  : a, H/ Ph; b,  $\text{CH}_3$ / Ph; c, Br/ Ph; d, Ph/,  $\text{CH}_3$



ence of piperidine or 2-aminopyridine as a base, the reaction yielded pyrazolo[5,1-*c*]-1,2,4-triazole derivative **173** (81M245).



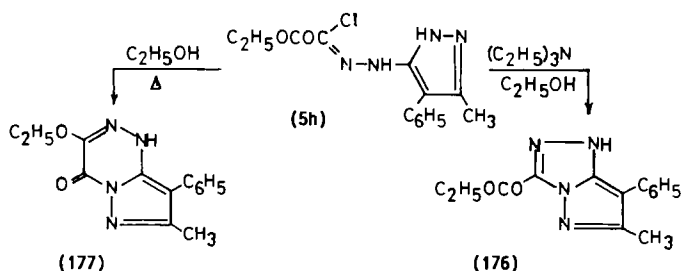
Cyclization of  $C$ -ethoxycarbonyl- $N$ -heteroarylhydrazonoyl chlorides **5** also led to different products according to reaction condition. Thus, the  $N$ -(5-pyrazolyl)hydrazonoyl chlorides **5f** and **g** cyclized readily to give **174a** and **b**, respectively, upon treatment with triethylamine in benzene



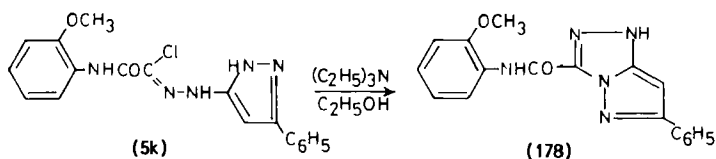
$R'/R''$  : a, H/ Ph; b, Ph/  $\text{NO}_2$

(77JHC227). However, cyclization of **5f,g** in the presence of methylamine or hydrazine hydrate gave **175a,b** instead (77JHC227).

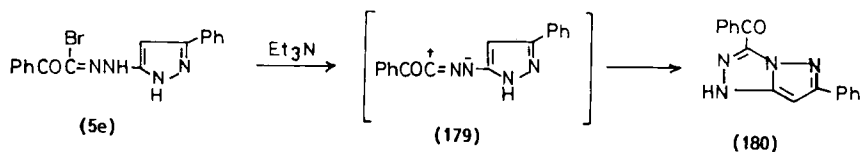
Furthermore, ethanolysis of chloride **5h** in the presence of triethylamine or 2-aminopyridine gave **176** (87AP850), whereas in the absence of base the reaction yielded pyrazolotriazine derivative **177** (87AP850). No explanation was given.

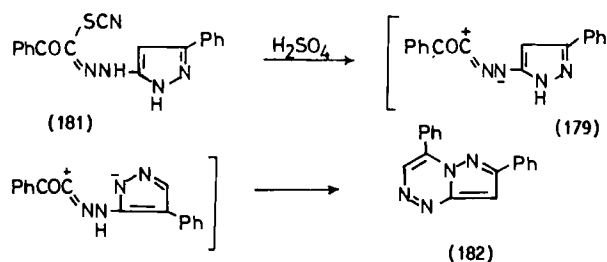


*N*-(3-Phenyl-5-pyrazolyl)-*C*-(2-methoxyphenyl)carbamoylhydrazonoyl chloride **5k** underwent intramolecular cyclization upon treatment with bases to give the pyrazolotriazole derivative **178** (77JHC227). Product **178** was also obtained by treatment of **5k** with methylamine or hydrazine hydrate in methanol (77JHC227).

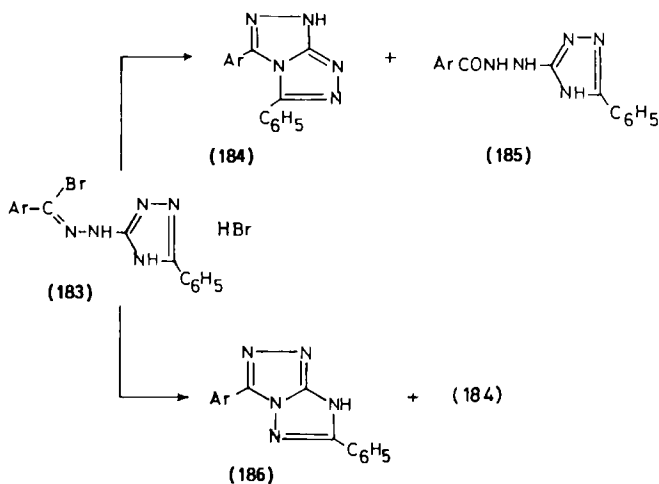


Electrocyclization of the nitrilimine intermediate **179** (87JHC1341) generated *in situ* from **5e** gave the pyrazolo[5,1-*d*]-1,2,4-triazole derivative **180**. In another report [78ZN(B)216] this same nitrilimine **179**, claimed to be generated by the action of concentrated sulfuric acid on **181**, yielded the pyrazolo[5,1-*c*]-*as*-triazine derivative **182** instead of the expected pyrazolo[5,1-*d*]triazole **180** (87JHC1341). The structure of the product **182** seems to need further investigation.



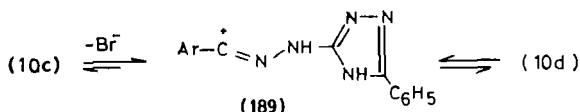
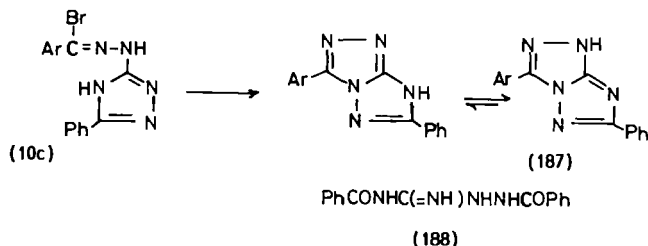


Dissolution of *N*-[3-phenyl-5-(1,2,4-triazolyl)]benzohydrazonoyl bromide hydrobromides **183** in 80% acetone–water (v/v) at 0°C yielded the [1,2,4]triazolo[3,4-*c*]-1,2,4-triazole **184** and the hydrazide **185** (65TL841). However, solvolysis of **183** in the presence of base at low temperature yielded a mixture of **184** and their isomers **186** (65TL841).

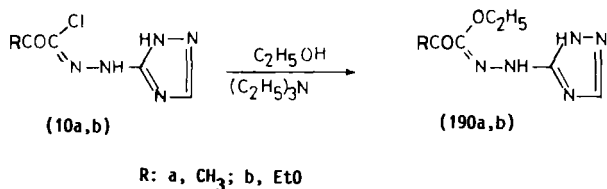


Treatment of **10c** with sodium acetate in acetic acid at reflux gave bicyclic compound **187** and 1,4-dibenzoylguanidine **188** in 5% and 15% yield, respectively (65TL841). The very small yield of **187** suggests either that triazolyl anchimerism is relatively ineffective or that, unlike the tetrazole ring, the 1,2,4-triazole moiety is a poor competitor (compared to solvent) for a nearby carbonium ion center (65TL841). On the other hand, in acid where the triazole ring is protonated, no 1,5-cyclization occurs; instead, a halogen exchange reaction occurs. For example, when bromides **10c** were treated with hydrochloric acid in dioxane–water, the correspond-

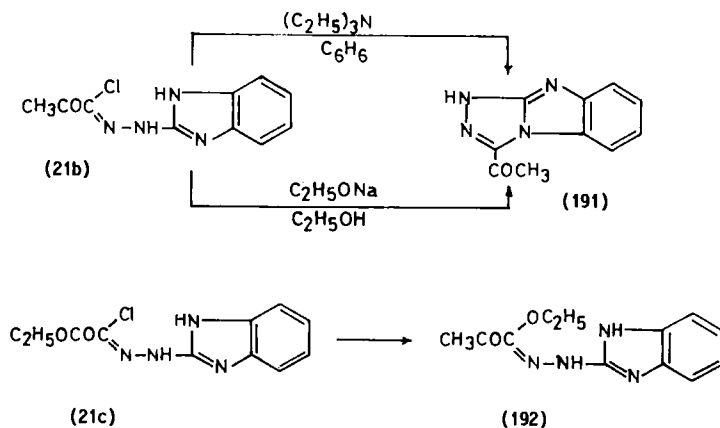
ing hydrazoneyl chlorides **10d** were produced (85%), presumably via the azacarbocation **189** [74JCS(P2)997].



*C*-Acetyl- and *C*-ethoxycarbonyl-*N*-(5-triazolyl)hydrazoneyl chlorides **10a** and **10b** did not cyclize upon refluxing in ethanol in the presence of triethylamine, but they yielded the ethyl hydrazoneate esters **190a** and **190b**, respectively (80JHC209).

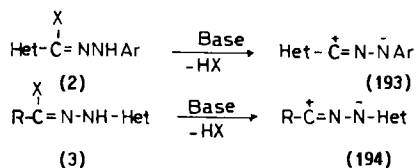


*N*-(2-Benzimidazolyl)hydrazoneyl chloride **21b** gave benzimidazo[2,1-*c*]-1,2,4-triazole **191** when heated in benzene in the presence of triethylamine (82MI1) or in ethanol in the presence of sodium ethoxide (83MI1). Contrary to this, *N*-(2-benzimidazolyl)-*C*-ethoxycarbonylhydrazoneyl chloride **21c** was reported (83MI1) to give the hydrazoneate ester **192** upon treatment with sodium ethoxide in ethanol. The expected cyclized product was not formed and no explanation was given for that ambiguous finding (83MI1).



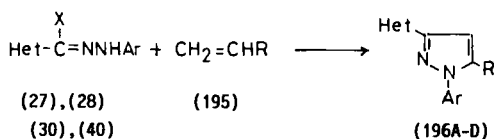
### B. 1,3-DIPOLAR CYCLOADDITION

Both *C*- and *N*-heteroarylhydrazonoyl halides **2** and **3** yield the corresponding nitrilimines **193** and **194**, respectively, when treated with a base in an aprotic solvent. When the latter 1,3-dipoles are generated in the presence of a suitable dipolarophile, they cycloadd and afford the corresponding cycloadducts. In all cases these cycloaddition reactions proved to be regioselective and stereospecific (84MI1).

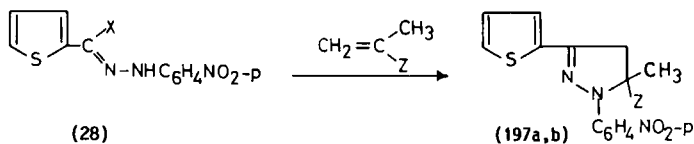


Thus, reactions of the *C*-heteroaryl-*N*-arylhydrazonoyl halides **27**, **28**, **30**, and **40** with acrylic acid derivatives **195** in chloroform in the presence of triethylamine yielded the corresponding 3-heteroaryl-5-substituted 2-pyrazoline derivatives **196** (70HCA1484; 87JHC1665; 88H695; 90JPR484, 90MI1). Also, reactions of **28** with  $\alpha$ -methylacrylic acid derivatives yielded the corresponding cycloadducts **197** (88H695).

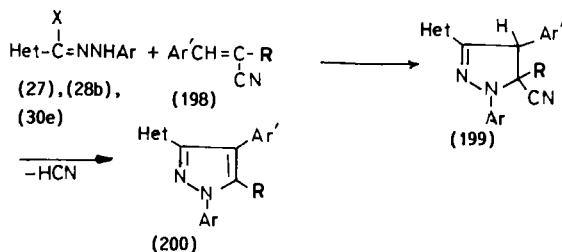
The 2-pyrazolines **199** arise from the reactions of *C*-heteroarylhydrazonoyl halides **27**, **28b**, and **30e** with  $\alpha$ -cyanocinnamic acid derivatives **198** in chloroform in the presence of triethylamine. In some cases, products **199** undergo elimination of hydrogen cyanide as soon as they are formed



R: a, CN; b, CONH<sub>2</sub>; c, COCH<sub>3</sub>



to give the corresponding pyrazole derivatives **200** (88CJC1386, 88H695, 88MI3; 90JPR484, 90MI1).

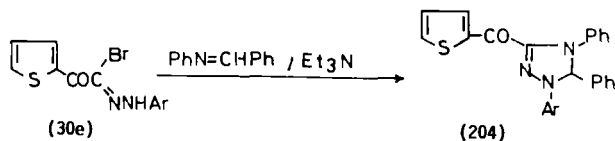
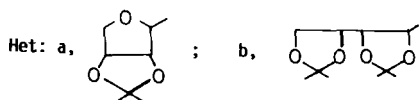
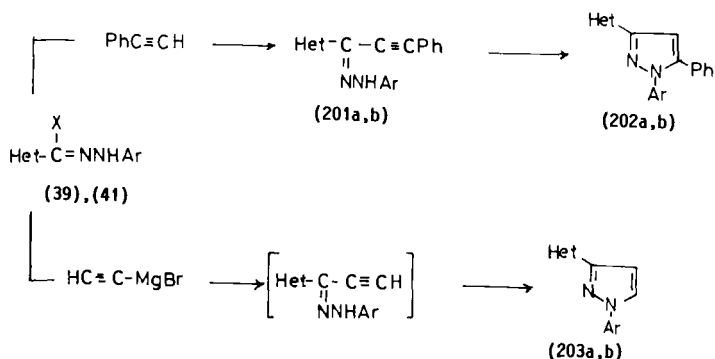


R: a, CN; b, COOEt; c, CONHPh

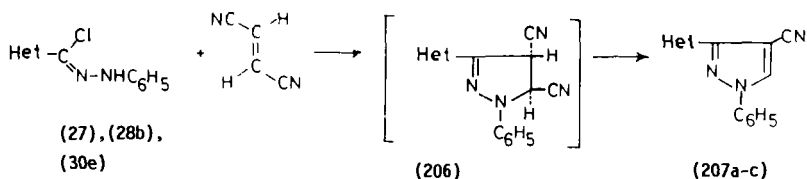
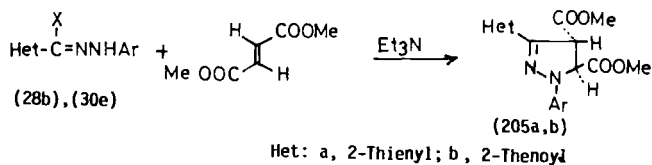
Phenylacetylene reacts with the hydrazonoyl halides **39** and **41** to afford the cycloadducts **202a** and **b**, presumably via cyclization of the intermediates **201a** and **b**, respectively (70HCA1484; 71HCA683). Pyrazole derivatives **202a** and **b** were also obtained by reacting each of the halides **39** and **41** with bromomagnesium phenylacetylide (71HCA683) (69HCA2569; 70HCA648). Likewise, reaction of the hydrazonoyl halides **39** and **41** with ethynylmagnesium bromide yielded the pyrazole derivative **203a,b** (69HCA2569; 70HCA648; 71HCA683).

Triazolines **204** arise from the reaction of benzaniline with hydrazonoyl halides **30e** [88PS(39)45].

Nitrilimines generated *in situ* from C-heteroarylhydrazonoyl halides **28b** and **30e** cycloadd to dimethyl fumarate to yield pyrazolines **205a** and **205b**, respectively (89MI2; 90JPR484). However, similar reactions of fumaronitrile with the C-heteroarylhydrazonoyl halides **27**, **28a**, and **30e** yielded the 4-cyanopyrazole derivatives **207a-c**, probably by elimination of hydro-

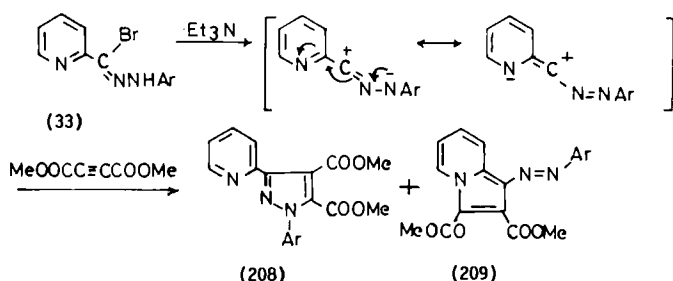


gencyanide from the initially formed cycloadducts **206a-c** (89SL275; 90JPR484, 90MI1).

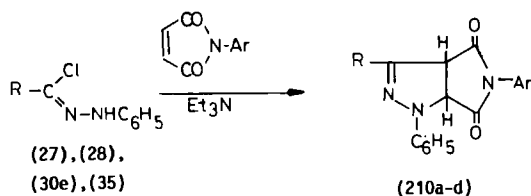


Het: a, 2-Furyl; b, 2-Thienyl; c, 2-Thenoyl

Reaction of the nitrilimine derived from *C*-(2-pyridyl)hydrazonoyl bromide **33** with dimethylacetylene dicarboxylate afforded a mixture of the usual 1,3-dipolar cycloadduct **208** and an unusual cycloaddition product **209** (81H717).

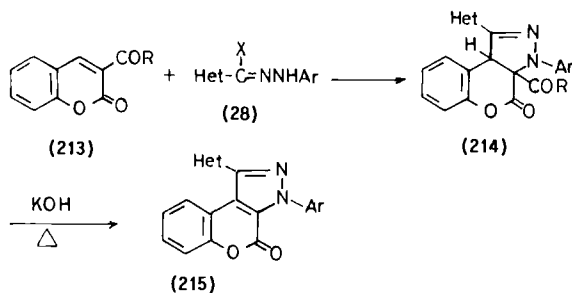
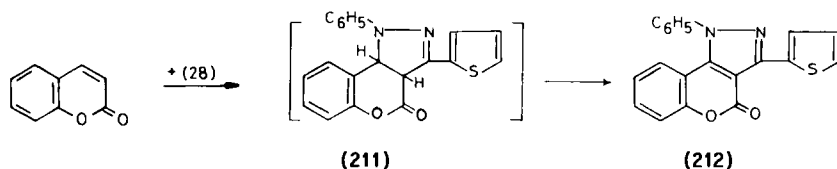


The cycloaddition of *N*-arylmaleimides to the nitrilimines generated from *C*-heteroarylhydrazonoyl halides **27**, **28a**, **30e**, and **35** yielded the cycloadducts **210a–d**, respectively [88PS(39)45; 89MI2; 90JPR484, 90MI1; 92AP205].



R: a, 2-Furyl; b, 2-Thienyl; c, 2-Thenoyl; d, 3-Benzisoxazolyl

Coumarin reacts with the *C*-heteroaryl-*N*-arylhydrazonoyl halides **28** in chloroform in the presence of triethylamine to produce cycloadduct **211**, which affords **212** upon oxidation (87JHC1665; 89MI3). On the other



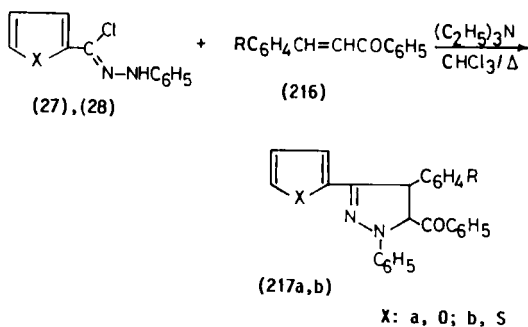
Het: 2-Thienyl

R: a, Ph; b, CH<sub>3</sub>

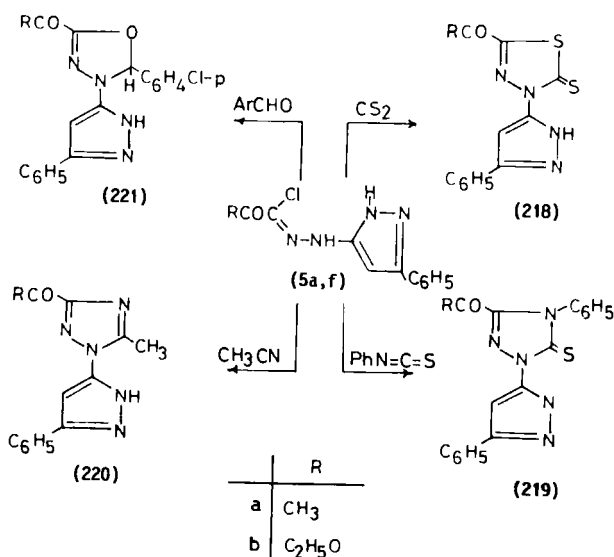


hand, 3-substituted coumarins **213** react with **28** under similar reaction conditions to give the regioisomeric cycloadducts **214** (89MI3). The structures of the latter were confirmed by their conversion to **215** (89MI3).

5-Aroyl-2-pyrazolines **217a,b** arise in good yield in the reaction of  $\alpha,\beta$ -unsaturated ketones **216** with the heterocyclic hydrazonoyl halides **27** and **28**, respectively (87JHC1665; 88H695, 88MI3; 90MI1).



The nitrilimines generated from *N*-(3-phenylpyrazol-5-yl)hydrazonoyl chlorides **5a,f** cycloadd carbon disulfide, phenylisothiocyanate, acetonitrile, and *p*-chlorobenzaldehyde in pyridine to provide the corresponding cycloadducts **218–221**, respectively (77HCA2171).

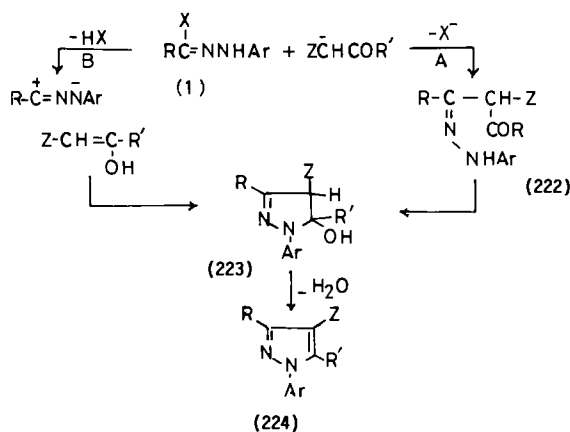


## C. REACTION WITH ACTIVE METHYLENE COMPOUNDS

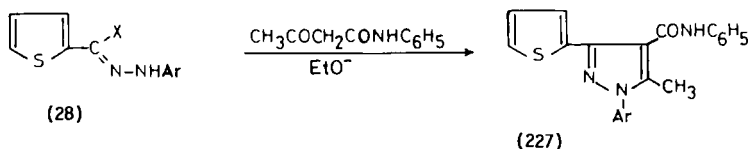
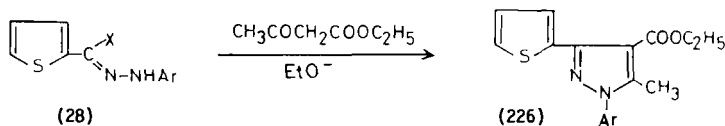
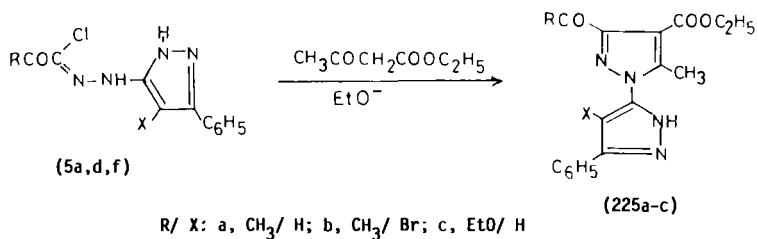
Both *C*-heteroaryl- and *N*-heteroarylhydrazonoyl halides react with the carbanions of various active methylene compounds to give the corresponding pyrazole derivatives **224**. Two possible pathways can account for such reactions (Scheme 2). Thus, route A involves nucleophilic attack at the hydrazonoyl carbon to give the acyclic hydrazone intermediate **222** followed by elimination of the elements of water. Alternatively, the nitrilimine derived from a hydrazonoyl halide cycloadds to the enol tautomer of the active methylene reactant to give the cycloadduct **223**, which in turn eliminates a water molecule to afford the end product **224** (route B). Although literature reports on these reactions have presented no distinction between these two possible routes, it seems to the authors that route A is the one that is operating under the conditions of the reactions studied, especially those of *N*-heteroarylhydrazonoyl halides. If route B were operating in the latter case, the nitrilimines generated would undergo either electrocyclic cyclization to give bicyclic products or dimerization to give the corresponding tetrazines. In all cases studied no products of either type were isolated under the reaction conditions employed.

For example,  $\beta$ -keto esters and  $\beta$ -keto anilides react with both *C*-heteroaryl- and *N*-heteroarylhydrazonoyl halides **5a,d,f** and **28a** to yield pyrazole derivatives **225–227** (77HCA2171; 80JHC209; 87JHC1665; 88H695).

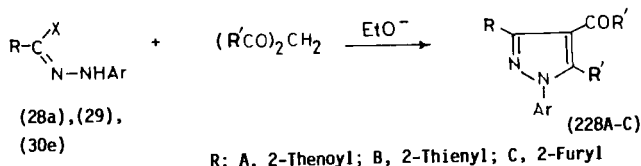
Similarly, *C*-heteroarylhydrazonoyl halides **28a**, **29**, and **30e** react with  $\beta$ -diketones such as acetylacetone and dibenzoylmethane to give the cor-



SCHEME 2

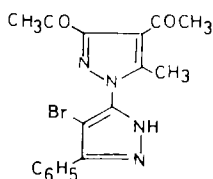


responding 4-acylpyrazole derivatives **228A–C** (82H57; 87JHC1665; 88H695, 880PP521).

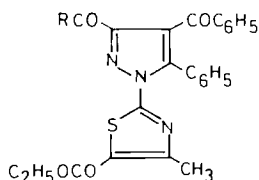


*N*-Heteroarylhydrazonoyl halides **5**, **9**, and **21b** also react with acetylacetone and dibenzoylmethane to give the corresponding 4-acyl pyrazole derivatives **229A–C**, respectively (80JHC209; 83MI1; 87MI2). However, reactions of acetylacetone with *N*-(3-phenyl-5-pyrazolyl)-*C*-acetyl and *C*-ethoxycarbonylmethanehydrazonoyl halides **5a** and **5f** were reported to give the acyclic substitution products **230a** and **b**, respectively (77HCA2171).

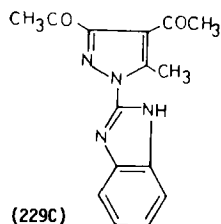
Reactions of *C*-(2-thienyl)hydrazonoyl halide **28a** with benzenesulfonylacetophenone afforded 4-arenesulfonyl-5-phenylpyrazole **231** (88H-695).



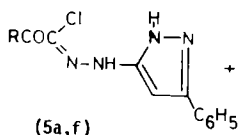
(229A)



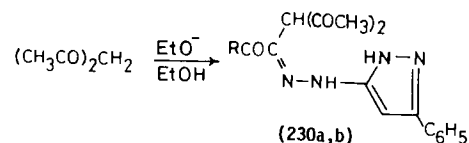
(229B)



(229C)

R: a, CH<sub>3</sub>; b, EtO

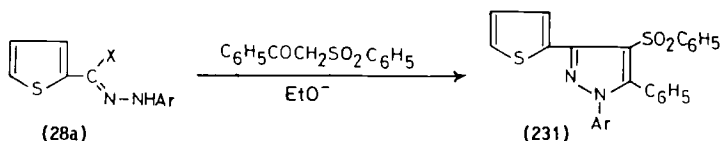
(5a,f)



(230a,b)

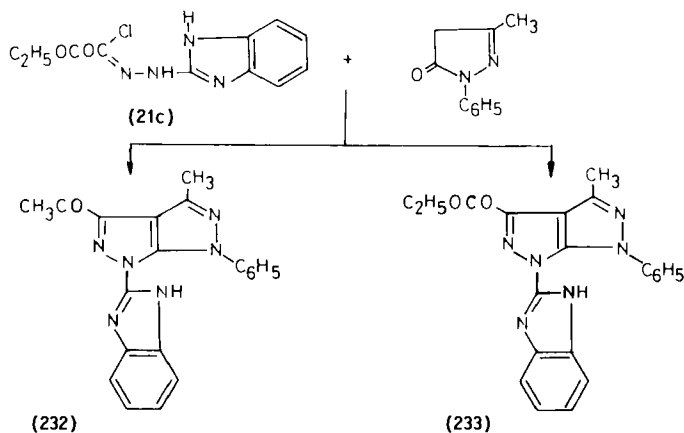
R: a, CH<sub>3</sub>; b, EtO

The product of the reaction of 3-methyl-1-phenyl-5-pyrazolone with chloride **21c** in ethanol in the presence of sodium ethoxide was assigned structure **232** (83MI1). Neither spectral nor elemental analysis data were given to support such an ambiguous assignment, however. As the 5-pyrazolone derivative is an active methylene compound, its reaction with hydrazonoyl halides **21c** is expected to give pyrazolo[3,4-*c*]pyrazole derivative **233**, not **232**.



(28a)

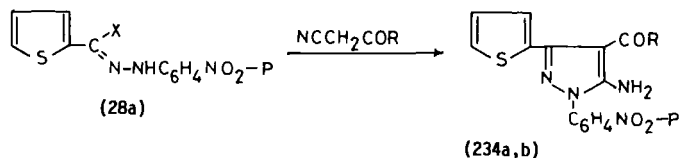
(231)



(232)

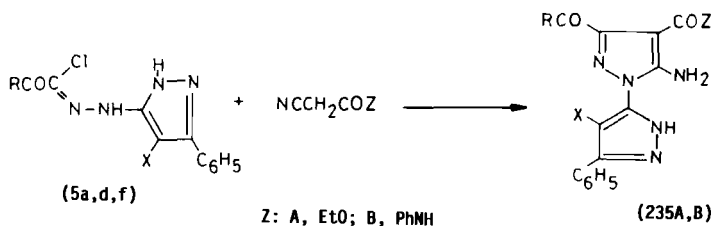
(233)

C-Heteroaryl- and N-heteroarylhydrazonoyl halides react with cyanoacetic acid derivatives to yield the corresponding 5-aminopyrazole derivatives. For example, reactions of C-(2-thienyl)-N-arylhydrazonoyl halide **28a** with ethyl cyanoacetate and cyanoacetanilide yielded the 5-aminopyrazole derivatives **234a** and **b**, respectively (88H695).

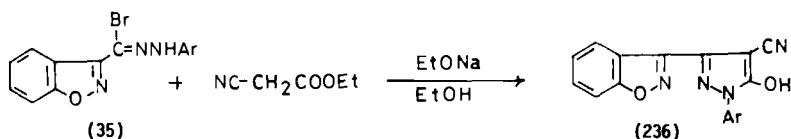


R: a, EtO; b, PhNH

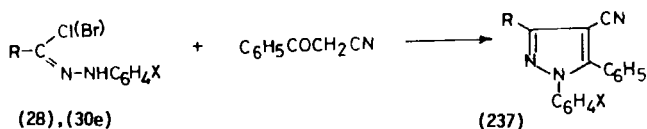
N-Heteroarylhydrazonoyl halides **5a,d,f** react in a similar manner with ethyl cyanoacetate and cyanoacetanilide to give the corresponding 5-aminopyrazole derivatives **235A** and **B** (77HCA2171; 80JHC209; 83MI1). In contrast, the reaction of the hydrazonoyl halide **35** with ethyl cyanoacetate was reported to yield 3-benzo[d]isoxazolyl-4-cyano-5-hydroxy-1-phenylpyrazole **236** in 59% yield [90ZN(B)1067].



Z: A, EtO; B, PhNH  
R/X: a,  $\text{CH}_3$ / H; b, EtO/ H; c,  $\text{CH}_3$ / Br

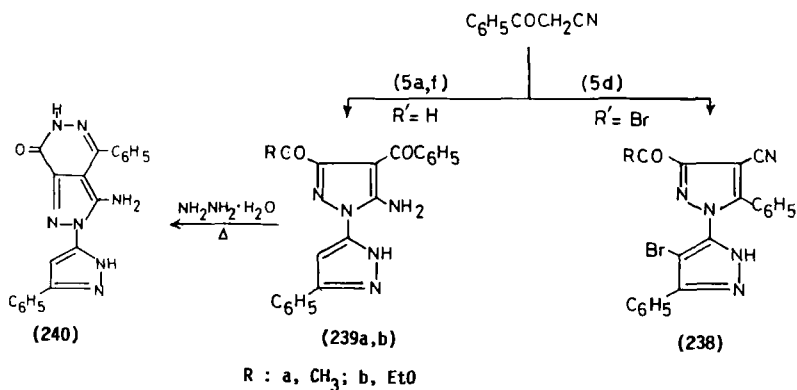


C-Heteroaryl-N-arylhydrazonoyl halides **28a** and **30e** react with benzo-ylacetonitrile in ethanol in the presence of sodium ethoxide to give 5-phenyl-4-cyanopyrazoles **237a** and **b**, respectively (87JHC1665; 88H695; 90JPR484).

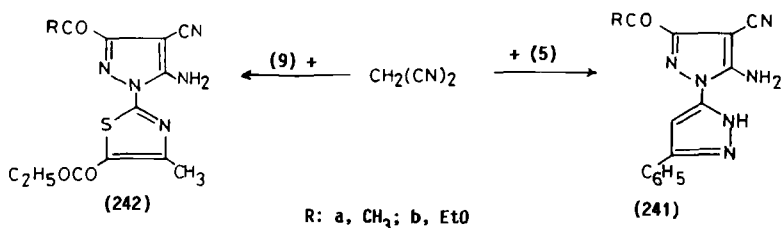


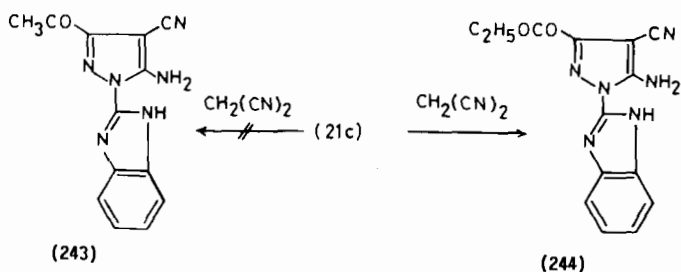
R: a, 2-Thienyl; b, 2-Thienyl

Different results were reported for the reactions of benzoylacetonitrile with *N*-heteroarylhydrazonoyl halides. Thus, while the reaction of benzoylacetonitrile with *N*-(3-phenyl-4-bromo-5-pyrazolyl)-*C*-acetylformohydrazonoyl chloride **5d** yielded the pyrazole derivative **238** (80JHC209), it was claimed that its reactions with *C*-acetyl- and *C*-ethoxycarbonyl-*N*-(3-phenyl-5-pyrazolyl)methanehydrazonoyl chlorides **5a** and **f** under similar reaction conditions afforded the pyrazole derivatives **239a** and **b** (77HCA2171). Hydrazinolysis of **239b** afforded the pyrazolopyridazine **240** (77HCA2171).



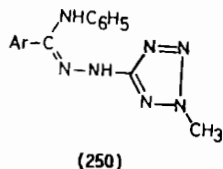
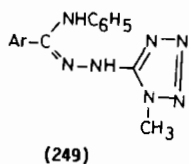
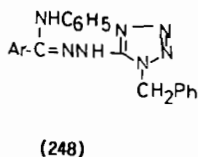
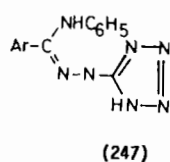
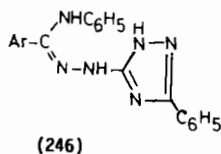
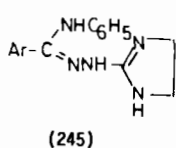
Malononitrile reacted with *N*-heteroarylhydrazonoyl halides **5** and **9** in ethanol in the presence of sodium ethoxide to yield the corresponding 5-amino-4-cyanopyrazole derivatives **241** and **242**, respectively [77HCA-2171; 88H695, 88PS(36)129; 91MI2]. The product of the reaction of *N*-(2-benzimidazolyl)-*C*-ethoxycarbonylformohydrazonoyl chloride **21c** with malononitrile was assigned structure **243** (83MI1). This assignment needs further confirmation as the product should have the structure **244**. Neither analytical nor spectral data were reported for the claimed product **243**.





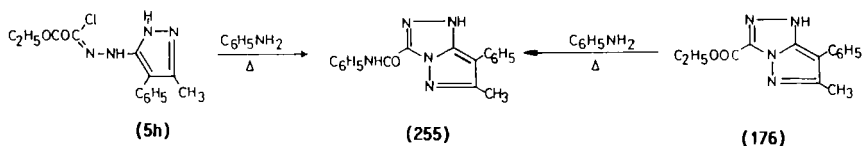
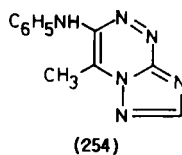
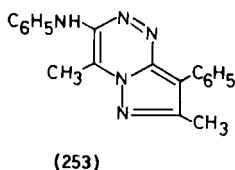
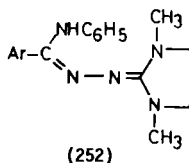
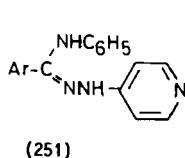
#### D. REACTION WITH AMINES

Reactions of aniline with heterocyclic hydrazonoyl halides were shown to be broadly useful in the preparation of the amidrazones **245–252** [67JCS(C)239; 68JCS(C)1711; 70TL4083; 71JCS(B)2198, 71JCS(C)2769; 72JCS(P1)2214, 72JCS(P1)2224; 73JCS(P2)1466; 74JCS(P2)997]. However, reactions of aniline with *C*-acetyl-*N*-(3-methyl-4-phenyl-5-pyrazolyl)hydrazonoyl halides **5l** and *C*-acetyl-*N*-(5-triazolyl)hydrazonoyl chloride **10a** furnished the pyrazolo[5,1-*c*][1,2,4]triazine derivative **253** (81M245) and the triazolo[5,1-*c*][1,2,4]triazine derivative **254** (80JHC209), respectively.

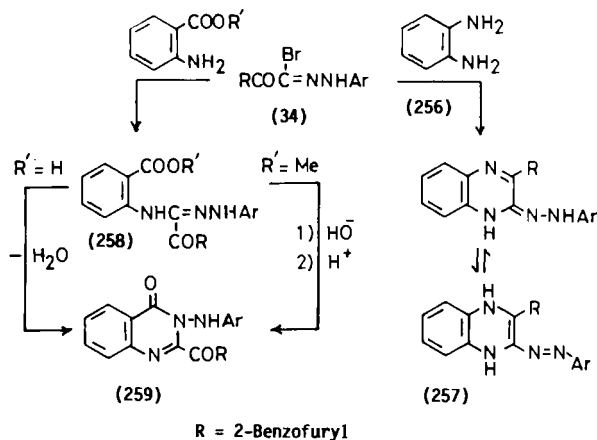


Heating **5h** with aniline leads to the formation of 6-phenylcarbamoyl-2-methyl-3-phenylpyrazolo[5,1-*c*][1,2,4]triazole **255** (87AP850). The structure of the latter was supported by its alternative synthesis from **176** and aniline (87AP850).

With *o*-phenylenediamine **256** the hydrazonoyl bromide **34** yielded the corresponding 2-arylaazo-3-benzofuryl-4(*H*)-1,4-benzopyrazine **257** (92-AP205). 3-Arylamino-2-benzofuroyl-4(3*H*)quinazolinones **259** were ob-

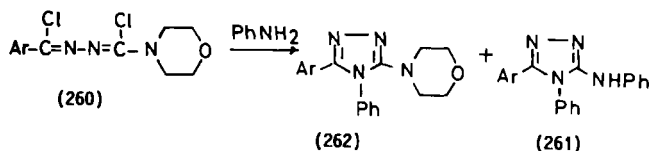


tained when compounds **34** were treated with anthranilic acid in ethanol in the presence of triethylamine (92AP205). Methyl anthranilate reacts with **34** to give the amidrazones **258** under similar conditions. Saponification of **258** followed by acidification yielded **259** (92AP205).

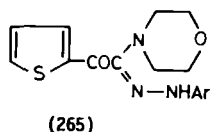
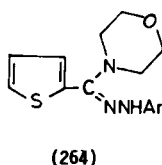
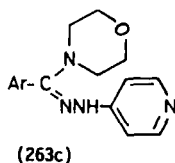
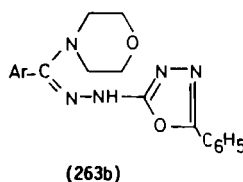
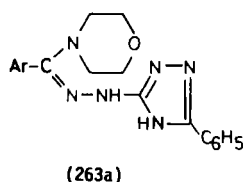


Treatment of the 1-aryl-1,4-dichloro-4-morpholinoamidrazones **260** with aniline gave the 3-anilino- and 3-morpholinotriazoles **261** and **262**, respectively, the former being formed by aniline displacement [72JCS(P1)2219].

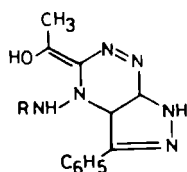




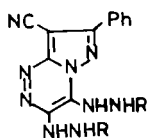
Secondary amines such as morpholine reacted with *N*-heteroaryl- (**11a**, **12**, and **15**) and *C*-heteroarylhydrazonoyl halides (**28a** and **30e**) to give the corresponding amidrazones **263a-c**, **264**, and **265**, respectively [72-JCS(P1)269; 73JCS(P2)1466; 74JCS(P2)997; 880PP521, 88PS(39)45].



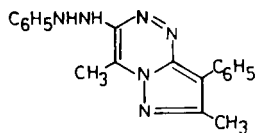
Conflicting results were obtained from the reactions of hydrazines with *N*-(5-pyrazolyl)hydrazonoyl halides **5d** and **5l**. Whereas reaction of hydrazine hydrate and phenylhydrazine with *C*-acetyl-*N*-(3-phenyl-4-bromo-5-pyrazolyl)methanehydrazonoyl chloride **5d** was reported to yield the pyrazolotriazine **266** (80JHC209), the reaction of phenylhydrazine with **5l** afforded the pyrazolo[5,1-*c*][1,2,4]triazine **268** (81M245). Furthermore, while the reaction of hydrazine hydrate and phenylhydrazine with *C*-ethoxycarbonyl-*N*-(3-methyl-4-phenyl-5-pyrazolyl)formohydrazonoyl halide **5h** afforded the pyrazolo[5,1-*c*][1,2,4]triazines **270** (87AP850), the reaction of hydrazine hydrate with **5f** was reported to give **269** (77JHC227). On the other hand, the reaction of **5i** with hydrazines yielded pyrazolotriazine **267** (92MI1).



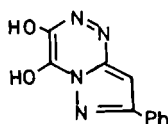
(266)



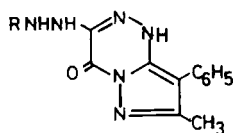
(267)



(268)



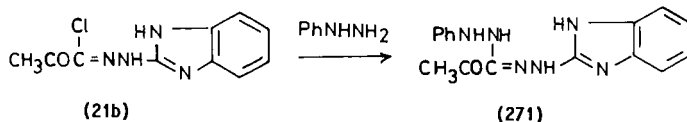
(269)



(270)

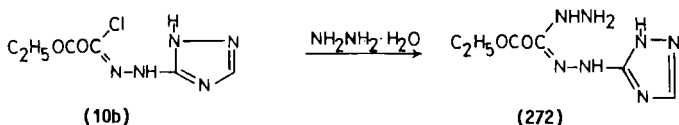
R: a, H; b, Ph

Reaction of *C*-acetyl-*N*-(2-benzimidazolyl)methanehydrazonoyl chloride **21b** with phenylhydrazine yielded a product that was assigned structure **271**. No spectral data were given to substantiate such an assignment, however (83MI1). Also, hydrazinolysis of **10b** with hydrazine hydrate gave the hydrazidine **272** (80JHC209).



(21b)

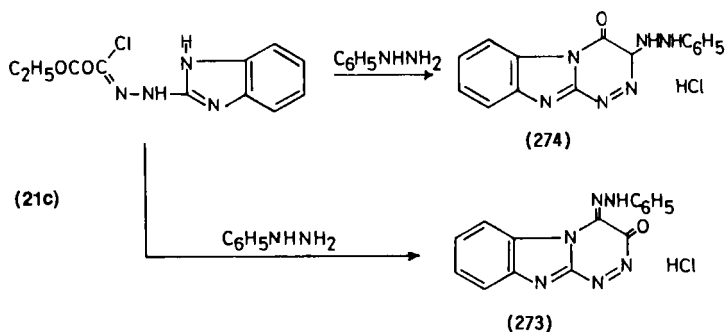
(271)



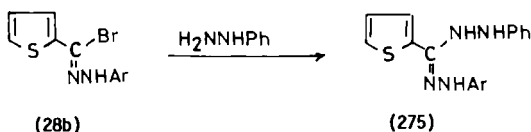
(10b)

(272)

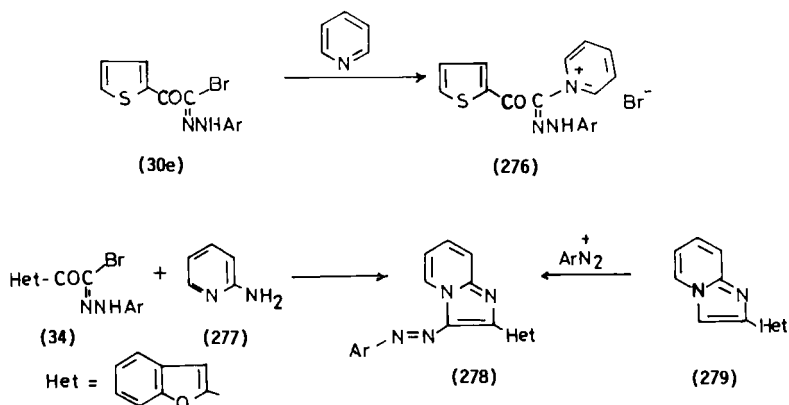
Treatment of *C*-ethoxycarbonyl-*N*-(2-benzimidazolyl)hydrazonoyl chloride **21c** with phenylhydrazine was reported (82MI1) to give hydrochloride salt **273**. Another report (83MI1) indicated that this same reaction afforded a product that was assigned structure **274**. The structure of this product needs to be reinvestigated.



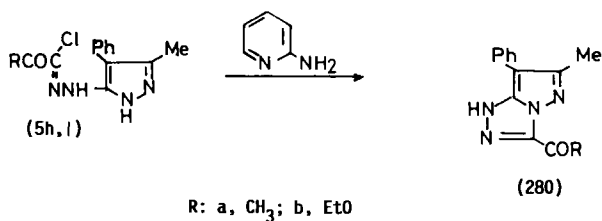
Treatment of **28b** with phenylhydrazine in ethanol gave the hydrazidine **275** (88H695).



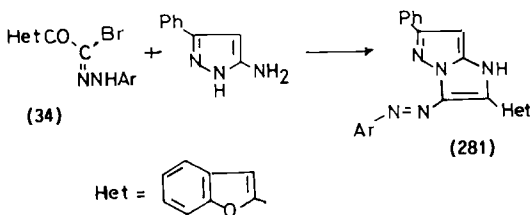
Pyridine reacts with *C*-(2-thenoyl)hydrazonoyl bromide **30e** [88PS(39)-45] to yield the pyridinium bromide **276**. 2-Aminopyridine **277** reacts, however, with **34** to give 2-benzofuryl-3-arylaazoimidazo[1,2-*a*]pyridine **278** (92AP205). The latter product was identified by its alternative synthesis by coupling the appropriate diazonium salt with 2-benzofurylimidazo[1,2-*a*]pyridine **279** (92AP205).



Reactions of *C*-acetyl- and *C*-ethoxycarbonyl-*N*-5-pyrazolylhydrazonoyl chlorides **5l** and **5h** with 2-aminopyridine yielded **280a** and **b** (81M245; 87AP850).

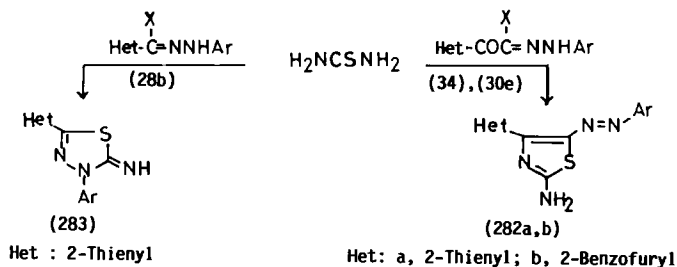


5-Amino-3-phenylpyrazole also reacted with **34** in ethanol to produce 1-phenyl-5-benzofuryl-4-arylazo-1*H*-pyrazolo[5,1-*a*]imidazoles **281** (92-AP205).



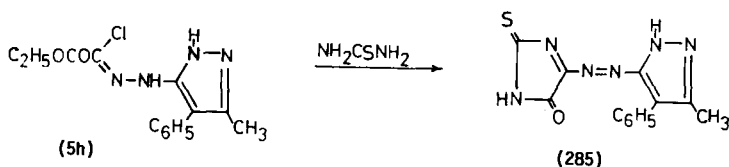
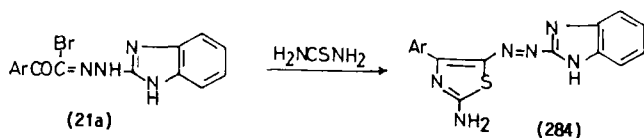
## E. REACTION WITH THIOUREA AND SELENOUREA

Reactions of hydrazonoyl halides with thiourea and selenourea were reported to give products that depend on the structure of the halide used. Thus, while reactions of thiourea with *C*-heteroacyl-*N*-arylhydrazonoyl halides **30e** and **34** yield the corresponding 5-arylazo-2-aminothiazole derivatives **282a** and **b** [88PS(40)243; 90MI3], its reaction with the halide **28b** gives 5-iminothiadiazoline derivatives **283** (88MI1).

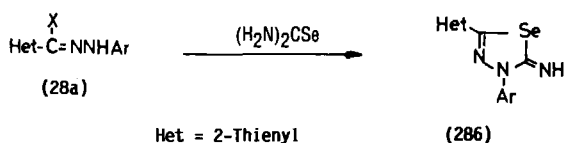


Also, reactions of thiourea with *N*-heteroarylhydrazonoyl halides were also reported to give different products depending on the nature of the *N*-heteroaryl moiety. For example, while *C*-aroyl-*N*-(2-benzimidazolyl)-hydrazonoyl halide **21a** reacted with thiourea to give the expected 2-amino-

4-aryl-5-(2-benzimidazolylazo)thiazoles **284** [90IJC(B)895], the reaction of *N*-(3-methyl-4-phenyl-5-pyrazolyl)hydrazonoyl halide **5h** with thiourea afforded the azo derivative **285** (87AP850).



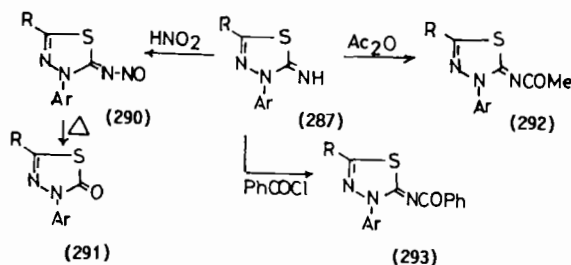
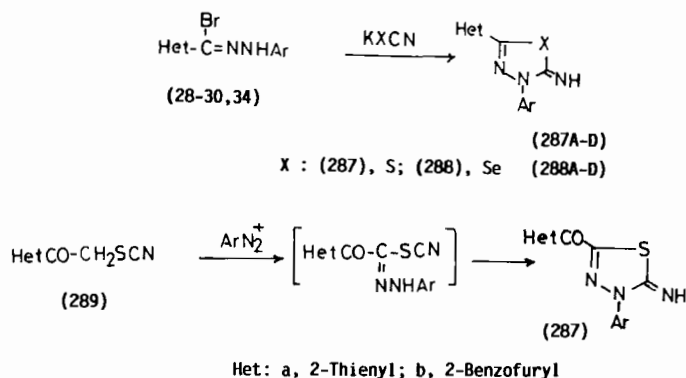
Selenourea reacts with **28a** to give the corresponding 5-iminoselenadiazolines **286** (88MI1).



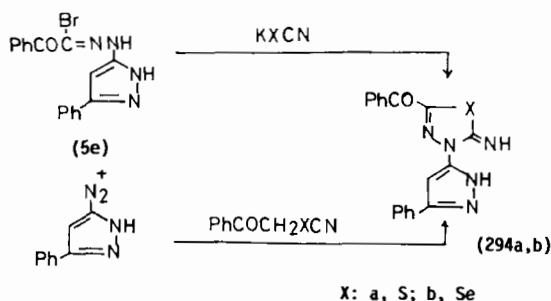
## F. REACTION WITH THIOCYANATE AND SELENOCYANATE ANIONS

Both *C*-heteroaryl- and *N*-heteroarylhydrazonoyl halides react with thiocyanate anion to give the corresponding thiadiazoline derivatives. For example, treatment of the *C*-heteroarylhydrazonoyl halides **28a**, **29**, **30e**, and **34** with potassium thiocyanate afforded the corresponding 1-aryl-3-heteroaryl-1,3,4-thiadiazolines **287A–D**, respectively [82H57; 88MI1, 88MI2, 88PS(39)45, 88PS(40)243; 90PSS(53)403; 91MI1]. Use of potassium selenocyanate in place of potassium thiocyanate afforded the selenadiazoline analogs **288** [88MI2, 88PS(40)243]. The structures of products **287A–D** were confirmed by their alternative synthesis by coupling of the corresponding  $\beta$ -keto thiocyanate **289** [88MI2, 88PS(39)45, 88PS(40)243; 90MI3] and by their chemical reactions outlined below. Thus, nitrosation of **287**

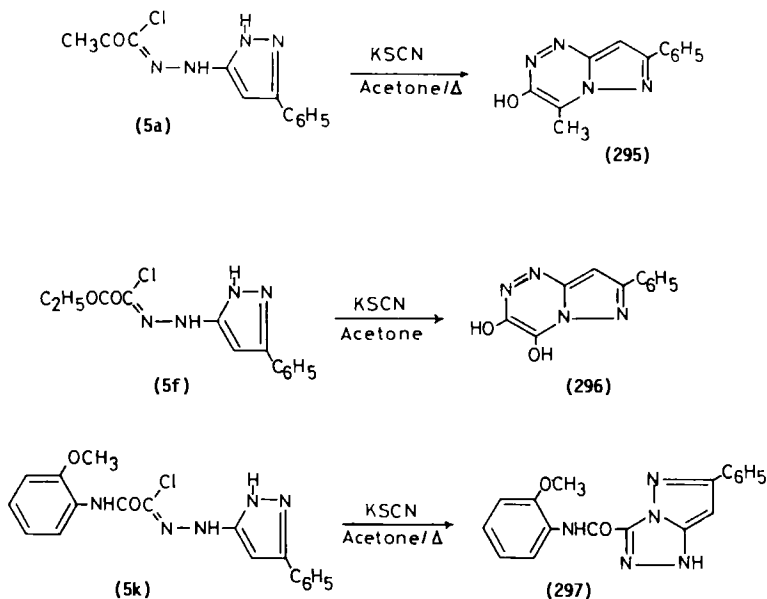
afforded the *N*-nitroso derivatives **290**, which lose nitrogen when heated in an inert solvent to give the thiadiazolinones **291**. Treatment of **287** with acetic anhydride and benzoyl chloride in pyridine yielded the corresponding *N*-acetyl- and *N*-benzoyl derivatives **292** and **293** respectively [88MI1, 88MI2, 88PS(39)45].



Likewise, *N*-heteroarylhydrazonoyl halide **5e** reacted with potassium thiocyanate and potassium selenocyanate to yield substitution products that cyclize directly to give the corresponding 1-heteroaryl-3-aroyl-5-iminothiadiazoles **294a** and selenadiazoles **294b** as the main products (87JHC1341). These products undergo nitrosation, acetylation, and benzylation to give the corresponding substitution products (87JHC1341).



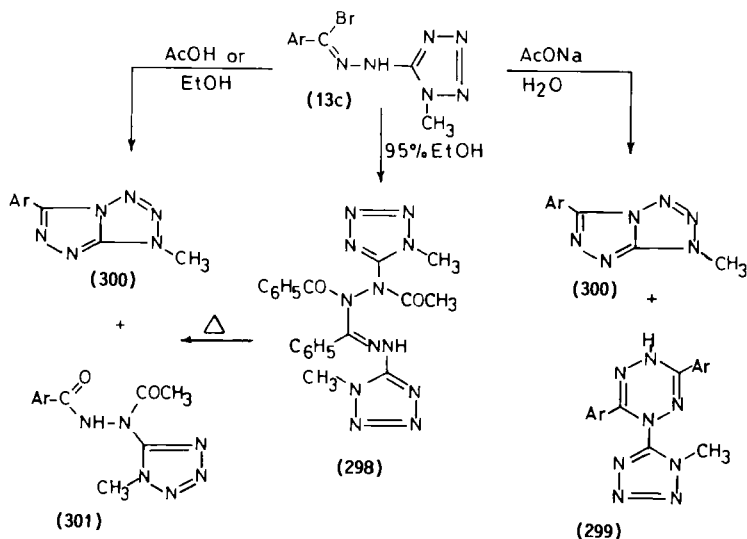
Reactions of potassium thiocyanate with *N*-(3-phenyl-5-pyrazolyl)hydrazonoyl chlorides **5a,f,k** gave products **295–297**, respectively. No rationalization was given to account for the formation of such unexpected products (77JHC227).



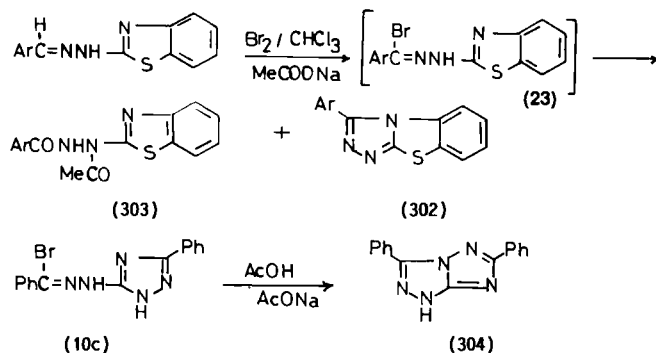
### G. REACTION WITH SODIUM ACETATE

Treatment of *N*-(1-methyl-5-tetrazolyl)benzohydrazonoyl bromides **13c** ( $\text{Ar} = \text{C}_6\text{H}_5$ ) with sodium acetate in 95% ethanol or acetic acid gave **298** and **299** in 56% and 7% yields, respectively [67JCS(C)239]. Heating **298** in benzene afforded the triazolotetrazole **300** and the tetrazole **301** [67JCS(C)239]. Similar treatment of substituted hydrazonoyl bromides **13c** ( $\text{Ar} = x\text{C}_6\text{H}_4$ ) with acetate ion in 95% ethanol afforded the corresponding derivatives **300** and **301** [67JCS(C)239].

With aqueous dioxane or aqueous acetone as the solvent, the role of the acetate ion is to buffer the hydrobromic acid eliminated during the reaction; **300** was then obtained as the major product (70–80%) under these conditions, with just a little (1–6%) of **299** being produced [67JCS(C)239].

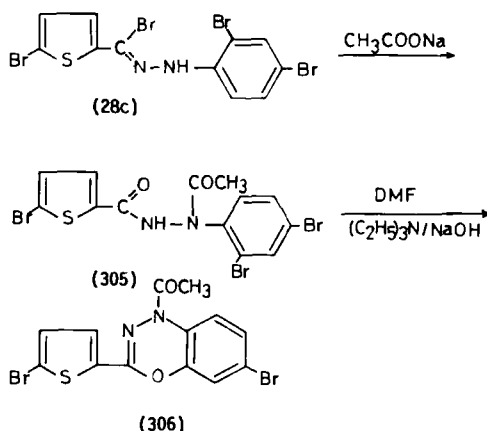


Reactions of the bromides **23** with sodium acetate afforded *s*-triazolo[3,4-*b*]benzothiazole **302** and *N*-acetyl hydrazides **303** [72JCS(P1)-1519]. Also, the triazotriazole **304** was obtained in 5% yield from treatment of **10c** with sodium acetate (65TL841).

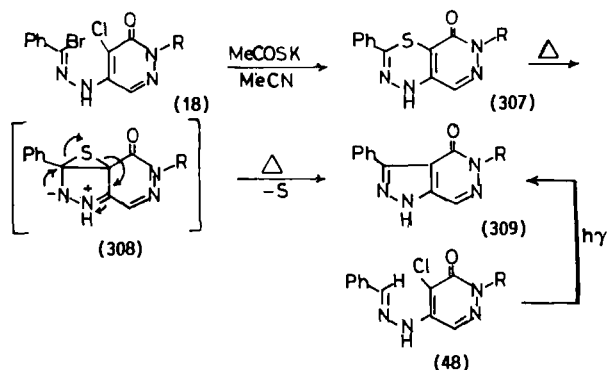


Similar treatment of the *C*-heteroarylhydrazonoyl bromide **28c** with sodium acetate in glacial acetic acid gave the hydrazide **305** in 85% yield. Heating **305** in dimethylformamide in the presence of bases afforded 4-acetyl-7-bromo-2-(5-bromo-2-thienyl)-4*H*-1,3,4-benzoxadiazine **306** in 6% yield [72JCS(P1)2915].



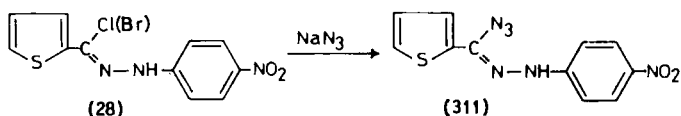
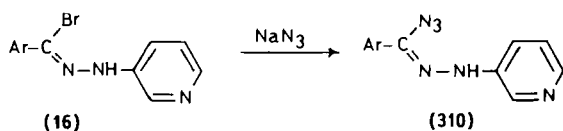


Reaction of the hydrazonoyl bromides **18** with potassium thioacetate gave 2-phenyl-4*H*-pyridazine [4,5-*c*]-1,3,4-thiadiazin-8(7*H*)-ones **307** (84CPB4437). Treatment of the latter products with a base in methanol at room temperature led to 5-substituted 3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)ones **309** (84H479). Also, heating **307** in dimethylformamide for 4 hours was reported by Kaji *et al.* to give **309** (84H479). Such ring contractions were assumed to involve **308** as an intermediate. Photolysis of the parent hydrazones **48** in benzene afforded pyrazolopyridazinones **309** in high yield (84H479, 84JHC1249).



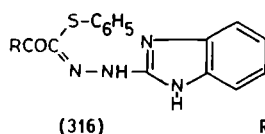
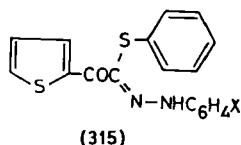
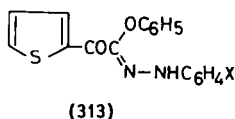
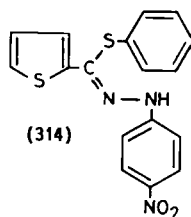
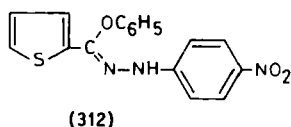
## H. REACTION WITH SODIUM AZIDE

Reaction of sodium azide with hydrazonoyl bromides **16** and **28** in acetone–water gave hydrazonoyl azides **310** and **311**, respectively, in good yields [72JCS(P2)1892; 88H695].



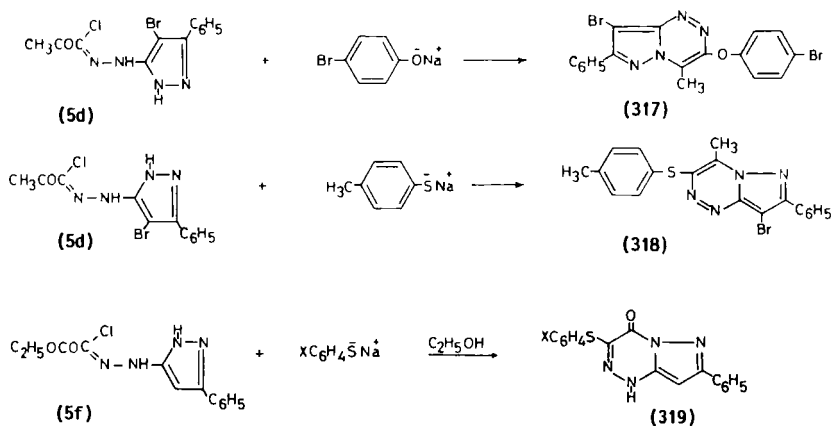
# I. REACTION WITH PHENOLS AND THIOPHENOLS

Hydrazonoyl halides have proved to be useful synthons for various hydrazone and thiohydrazone esters. Thus, the hydrazones **312** and **313** and the thiohydrazones **314**–**316** have been prepared in good yields by the reaction of the corresponding hydrazonoyl halides with sodium phenolate and sodium thiophenolate, respectively [83MI1; 88H695, 880PP521, 88PS(39)45; 91MI1]. However, reactions of chloride **5d** with *p*-bromophenolate and *p*-methylthiophenolate anions yielded the pyrazo-

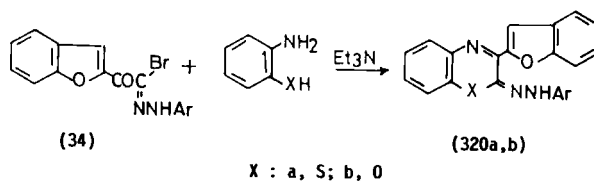


R : a, CH<sub>3</sub>; b, EtO

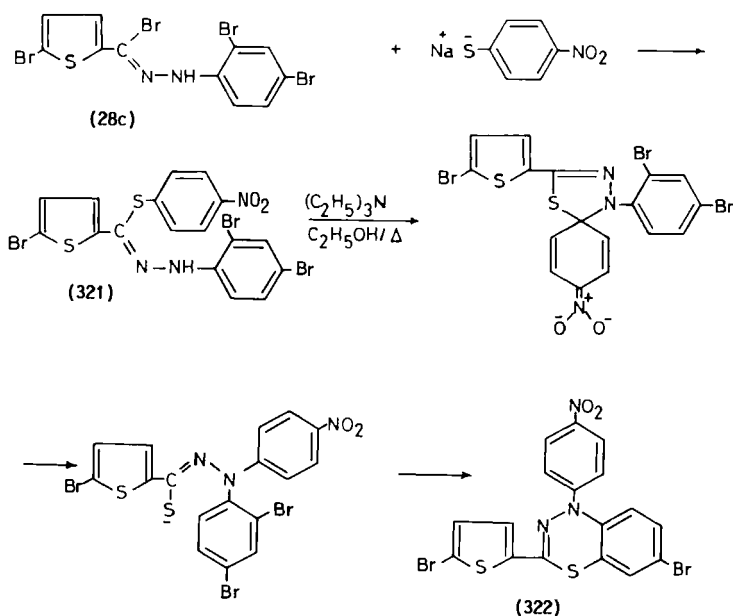
lotriazine derivatives **317** and **318**, respectively (80JHC209). Also, *N*-5-(3-phenylpyrazolyl)hydrazonoyl chlorides **5f** reacted with thiophenolate anions to afford the pyrazolo[1,5-*c*]-*as*-triazin-7-one derivative **319** (77JHC227).



2-Arylazo-3-benzofuryl-4(*H*)-1,4-benzothiazine **320a** (92AP205) and 1,4-benzoxazine derivative **320b** (92AP205) have been prepared by the reaction of the hydrazonoyl bromide **34** with *o*-aminothiophenol and *o*-aminophenol, respectively.

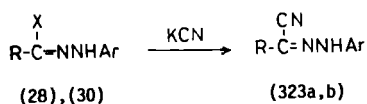


The thiohydrazonate ester **321** obtained from reaction of bromide **28c** and sodium *p*-nitrothiophenolate was converted to thiadiazine derivative **322** when it was refluxed with triethylamine in ethanol (75CJC1484).



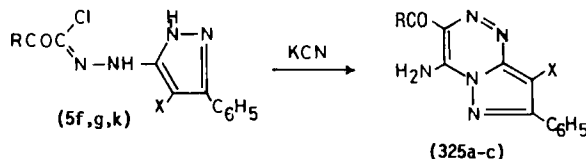
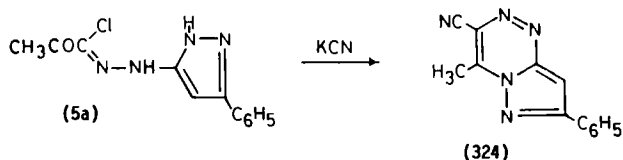
## J. REACTION WITH POTASSIUM CYANIDE

The reaction of *C*-heteroarylhydrazonoyl halides with potassium cyanide is straightforward, leading in all cases to the corresponding substitution products. For example, the halides **28** and **30e** yielded the cyanohydrazones **323a** and **b**, respectively, upon treatment with potassium cyanide in ethanol at room temperature [88H695, 88PS(39)45].



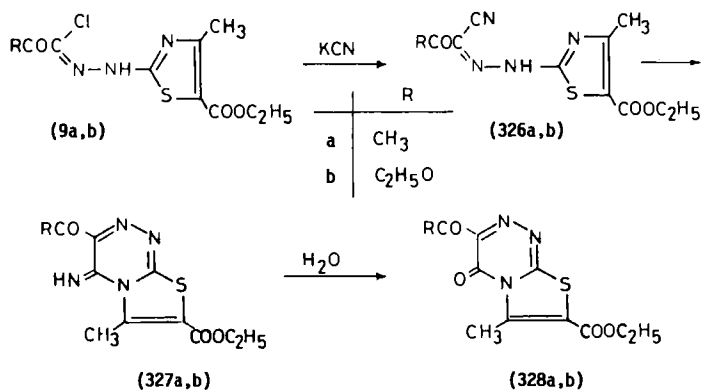
R: a, 2-Thienyl; b, 2-Thienyl

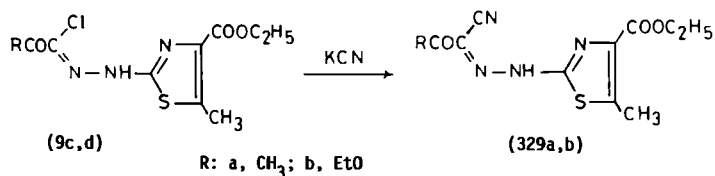
Reaction of *N*-5-(3-phenylpyrazolyl)hydrazonoyl chlorides **5** with potassium cyanide in ethanol were reported to give different products. Thus, whereas reaction of **5a** with potassium cyanide yielded **324** (77JHC227), reactions of *N*-(5-pyrazolyl)hydrazonoyl chlorides **5f** (77JHC227) and **5g** (89MI1) yielded the pyrazolo-*as*-triazine derivatives **325a** and **b**. Also, reaction of potassium cyanide with **5k** yielded **325c** (77JHC227).



R / X : a, EtO/H; b, EtO/ NO<sub>2</sub>; c, 2-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>NH/H

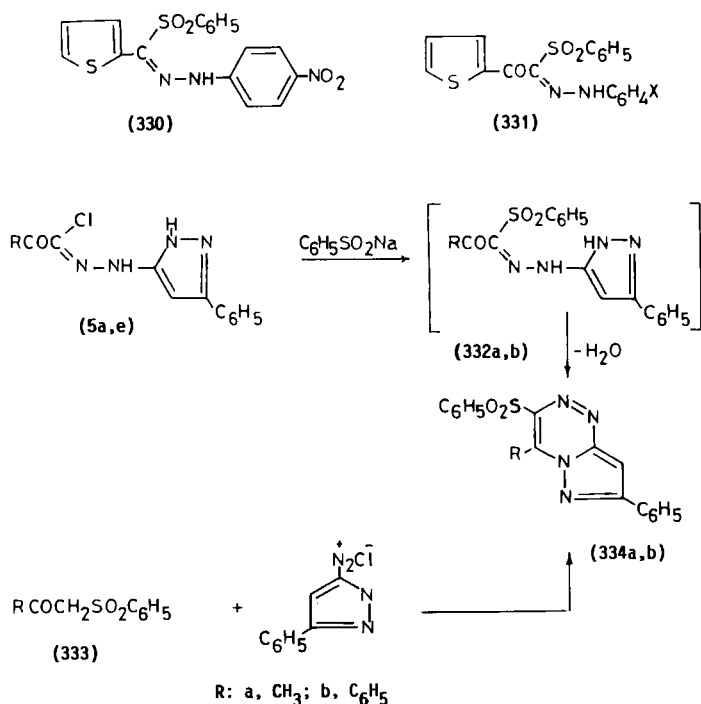
Contradictory results were also reported for the reactions of potassium cyanide with *N*-thiazolyldiazonoyl chlorides. Thus, reaction of the chlorides **9a** and **b** with cyanide anion in ethanol yielded the iminothiazolotriazine derivatives **327a** and **b** via cyclization of the substitution products **326a** and **b**, respectively. Products **327a** and **b** hydrolyze readily to give the triazinone derivatives **328a** and **b**, respectively [87MI2; 89MI1; 91MI3]. On the other hand, reaction of the isomeric thiazolyldiazonoyl chloride **9c** and **d** with potassium cyanide in refluxing acetone gave only the substitution products **329a** and **b**, respectively (83JHC285). This latter result should be accepted with reservation, since the chlorides **9c** and **d** should be **9a** and **b**, respectively, as outlined earlier (Section II,B).



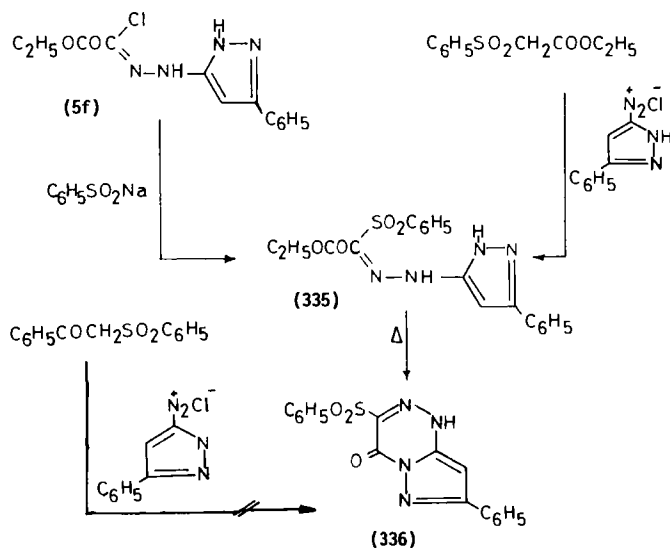


## K. REACTION WITH SODIUM BENZENESULFINATE

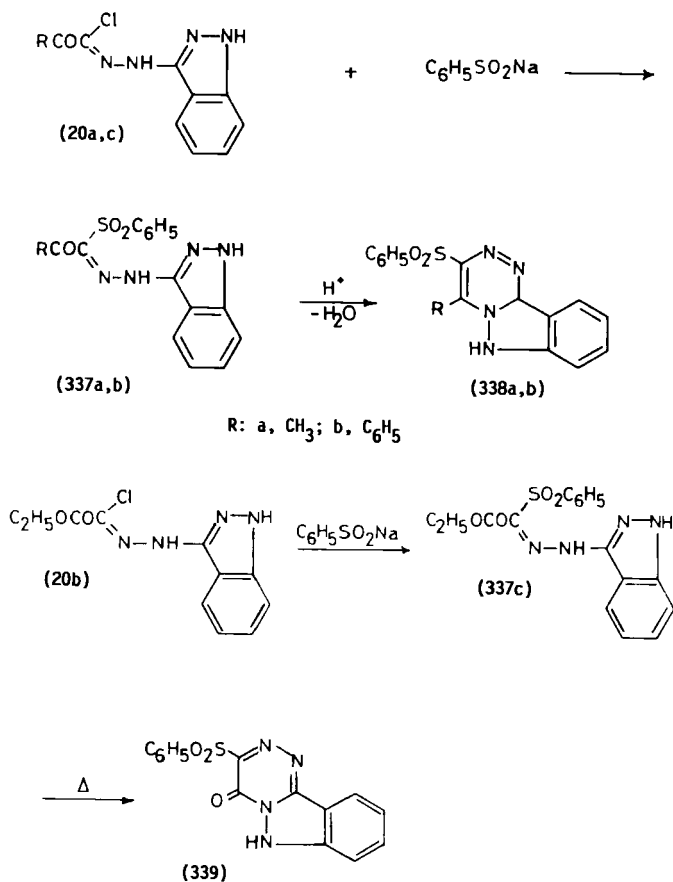
Reactions of the hydrazonoyl halides **28a** and **30e** with sodium benzenesulfinate afforded the corresponding substitution products **330** and **331**, respectively (88H695, 88OPP521). However, reactions of **5a** and **e** with sodium benzenesulfinate in ethanol at room temperature afforded the pyrazolotriazines **334a** and **b**, respectively (85JHC453). These results indicate that the intermediate hydrazones **332a,b** undergo cyclization as soon as they were formed. Thus, **334a** and **b** were obtained directly by coupling of diazotized 3-phenyl-5-aminopyrazole to the corresponding  $\beta$ -ketosulfones **333a** and **b**, respectively (85JHC453).



Similar reaction of *N*-(3-phenyl-5-pyrazolyl)-*C*-ethoxycarbonylhydrazonoyl chloride **5f** with sodium benzenesulfinate in ethanol at room temperature, however, gave substitution product **335**, which is identical in all respects with an authentic sample prepared by coupling diazotized 3-phenyl-5-aminopyrazole with ethyl benzenesulfonyl acetate (85JHC453). When the reaction of **5f** with sodium benzenesulfinate in ethanol was carried out under reflux, it yielded the pyrazolotriazinone **336**. The latter product was also obtained by heating **335** in an oil bath at 200°C (85JHC453). In one report, it was erroneously stated that product **336** can also be obtained from coupling of benzenesulfonylacetophenone with diazotized 3-phenyl-5-aminopyrazole (77JHC227).

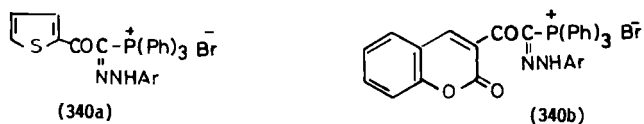


Likewise, the sulfonylhydrazones **337a–c** prepared from reactions of sodium benzenesulfinate with hydrazonoyl chlorides **20a–c** in ethanol at room temperature cyclized *in situ* to give **338a**, **338b**, and **339**, respectively (87MI1).



## L. REACTION WITH TRIPHENYLPHOSPHINE

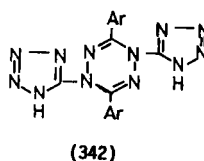
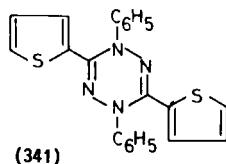
The phosphonium bromides **340a** and **b** have been isolated in good yield from the reactions of the hydrazonoyl bromides **30e** and **38** with triphenylphosphine, respectively [88PS(39)45; 91MI1].





## M. DIMERIZATION

When chloride **28a** was treated with a base in the absence of a suitable dipolarophile, the resulting nitrilimine dimerized to give 1,4-diphenyl-3,6-(di-2-thienyl)-1,4-dihydro-1,2,4,5-tetrazine **341** (87JHC1665). Also, tetrazine derivatives **342** were isolated on heating hydrazonoyl bromides **13b** in 50% aqueous ethanol (57JOC692).



## V. Conclusion

From the foregoing survey of heterocyclic hydrazonoyl halides, it appears that the main emphasis has been restricted to both their preparation and use as intermediates for further synthesis. Large areas of their chemistry, particularly regarding their physical and biological properties, remain to be developed. A deeper understanding of some aspects of their 1,3-dipolar cycloaddition reactions, such as regiochemistry and site selectivity in terms of the frontier molecular orbital method, is also needed.

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## Cycloaddition Reactions with Vinyl Heterocycles

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## I. Introduction

The Diels–Alder reaction is one of the most common and elegant methods for the construction of six-membered rings. Its versatility can be understood by looking at the range of dienes of dienophiles to which this reaction has been extended.

Dienes and dienophiles should have complementary electronic character. In the majority of reported examples the diene bears electron-donating substituents, and the dienophile electron-attracting substituents. In a small number of reactions, known as Diels–Alder reactions with inverse electron demand, an electron-deficient diene reacts with an electron-rich dienophile. The first group of reactions has been studied thoroughly with important modifications that affect the complementary electronic character of the diene and dienophile or the steric requirements.

Although the number of Diels–Alder cycloadditions with open-chain and alicyclic dienes is very large, the number of examples with aromatic heterocyclic compounds is relatively small. The introduction of a vinyl group as a substituent onto a heterocycle increases the number of possibilities of reaction. This new possibility, however attractive for synthetic purposes, is successful, with a few exceptions, only with  $\pi$ -excessive five-membered heterocyclic derivatives. As is usual in this kind of reaction, Michael additions, “ene” reactions, [2 + 2]-cycloadditions, and polymerization compete with the Diels–Alder cycloaddition.

## II. Reactions of Vinyl Heterocycles with Carbodienophiles

### A. REACTIONS WITH ACETYLENIC ESTERS

#### 1. *Vinylfurans*

The endocyclic and exo–endo diene systems of 2-vinylfuran **1a** participate in cycloaddition reactions with dimethyl acetylenedicarboxylate

(DMAD), and a 1 : 1 mixture of the diesters **2a** (endocyclic product) and **4a** (exo-endo product) was obtained when the reaction was carried out at room temperature. The overall yield (10%) was very low due to polymerization of the 2-vinylfuran. In contrast with reactions with other dienophiles (see Section II,B,1), in which the exo-endo diene of 2-vinylfurans proved to be more reactive than the furan system itself, the reaction with DMAD resulted in reduced selectivity, probably due to equilibration of the more soluble adducts in this case (68TL4589; 73AJC1059).

When the reaction was carried out at 80°C, benzofuran **4a** and a 1 : 2 adduct **5a** were isolated. The formation of **5** is the result of an ene reaction of intermediate **3** with a second molecule of DMAD.

The reaction of 2-vinylfuran **1a** with methyl propiolate (MP) did not proceed at room temperature owing to the lower reactivity of this dienophile; and at 80°C, although two isomeric benzofurans are possible, only methyl benzofuran-4-carboxylate **6a** was obtained. This regioselectivity is not unexpected, considering electronic and substituent effects (67AG16).

As 2-vinylfuran rapidly polymerizes even in a nitrogen atmosphere in the presence of a stabilizer, yields obtained for these Diels-Alder reactions were very low. In fact, when the more stable 5-(4-nitrophenyl)-2-vinylfuran **1b** reacted with DMAD, the yield of the aromatized cycloadduct, dimethyl 2-(4-nitrophenyl)benzofuran-4,5-dicarboxylate **4b**, was 50%. The 4-nitrophenyl group not only deactivated the vinylfuran for oxidation and polymerization, but also deactivated the diene system toward cycloadditions, and the reaction was successful only when conducted in boiling xylene. The decrease in reactivity of the reactive diene may account for the relatively low yield of methyl 2-(4-nitrophenyl)benzofuran-4-carboxylate **6b** obtained in a similar reaction with MP (73-AJC1059).

2-Isopropenylfuran **1c** reacted with acetylenic esters, affording only Diels-Alder adducts, and no products from the addition to the diene ring could be isolated (73AJC1059). Thus, the reaction with DMAD afforded dimethyl 7-methylbenzofuran-4,5-dicarboxylate **4c**, while the reaction with MP gave methyl 7-methylbenzofuran-4-carboxylate **6c**. In both cases, higher yields were obtained than in the corresponding reactions with 2-vinylfuran. According to the authors, the more favorable *cis* orientation of the diene system could account for this enhancement.

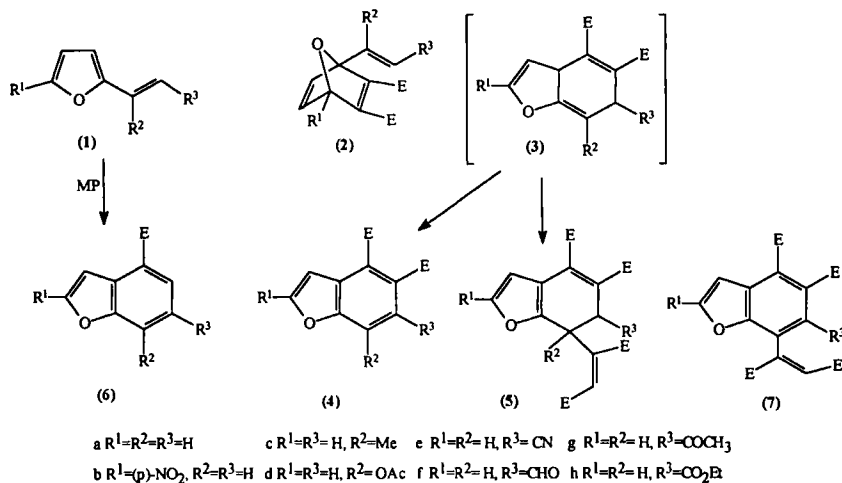
In reactions of the enol acetate, 2-(1-acetoxyvinyl)furan **1d** with DMAD, both of the alternative diene systems reacted with the dienophile, and a mixture of dimethyl 7-acetoxybenzofuran-4,5-dicarboxylate **4d** and dimethyl 3-(1-acetoxyvinyl)-3,6-epoxy-3,6-dihydrophthalate **2d** was obtained (73AJC1059).

Although it was reported that 2-vinylfurans having electron-withdrawing



$\beta$ -substituents on the vinyl group did not react with DMAD (83JOC2488), this reaction was reexamined to see if more vigorous reaction conditions could force the reaction (91MI1). Thus, when a mixture of the 2- $\beta$ -substituted vinylfurans **1e–g** and DMAD was heated in a stainless steel reaction vessel at 185°C, the corresponding substituted benzofurans **4e–g** were obtained in moderate yields (30%). No similar adduct **4h** was isolated from the reaction of **1h** and DMAD.

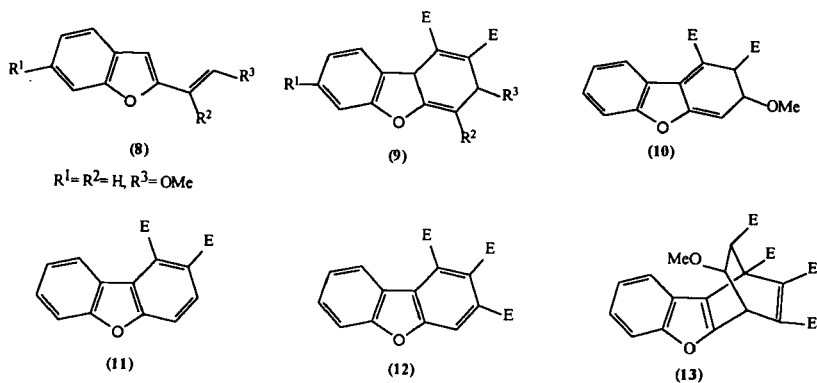
Because the rate of reactions having a large negative activation volume is accelerated under high-pressure conditions, the cycloaddition reactions of vinylfurans, whose reported yields were extremely poor even after long reaction times, were investigated at 15 kbar (81JOC5454). In all the reactions with DMAD the benzofurans were obtained as the main products, and no adducts from addition to the furan-ring diene system were detected. In the reaction of **1d** with DMAD, a 1 : 2 adduct **7a** was obtained as a result of an ene reaction of a second molecule of the ester to the intermediate **3** and subsequent elimination of acetic acid. As expected, the yield of **7a** was raised when the molar ratio of DMAD to **1d** was increased.



## 2. Vinylbenzofurans

As many naturally occurring dibenzofurans possess a 3-hydroxy substituent, the reactions of *trans*-2-(2-methoxyvinyl)benzofuran **8** were studied (68TL4589; 70AJC2119). The reaction with DMAD yielded three products, none of which had the expected structure **9**. The major product was

dimethyl 3-methoxy-2,3-dihydrobenzofuran-1,2-dicarboxylate **10**, formed by rearrangement of the initial adduct **9** and promoted by an excess of the dienophile (69TL351; 70T210). The major by-product of the reaction was dimethyl dibenzofuran-1,2-dicarboxylate **11**, probably formed by a 1,4-elimination of methanol from the rearranged adduct **10** with concomitant aromatization. The third, and minor, by-product was trimethyl dibenzofuran-1,2,3-tricarboxylate **12**. Its formation can be explained by a retro-Diels–Alder reaction of the bis adduct **13**.

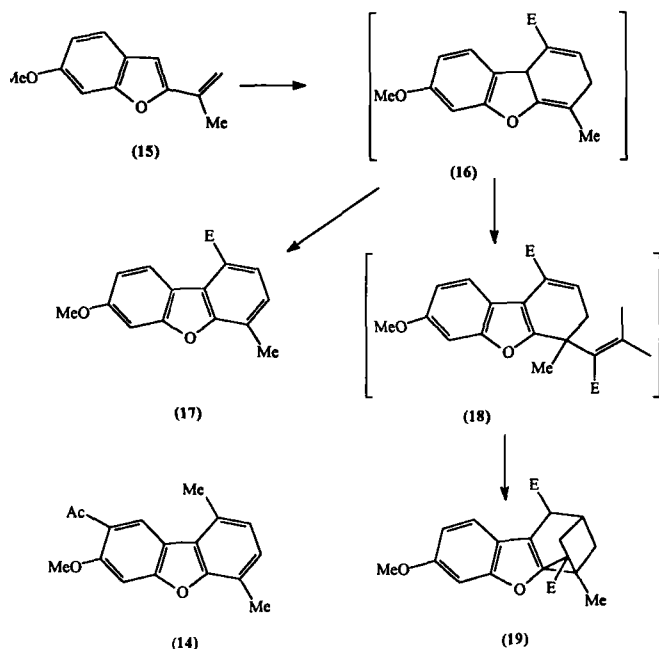


The reaction of vinylbenzofurans has also been used for the preparation of a natural product extracted from the roots of *Ruscus aculeatus* L., ruscodibenzofuran **14**, which exhibits medicinal properties [80CC1103; 83JCS(P1)2927]. In the reaction of 2-isopropenyl-6-methoxybenzofuran **15** with MP, the dibenzofuran **17** necessary for the preparation of ruscodibenzofuran **14** was obtained along with another compound **19** that remained unidentified [83JCS(P1)2927]. A few years later, the structure of **19** was elucidated using a combination of isotopic labeling studies and two-dimensional <sup>1</sup>H and <sup>13</sup>C NMR experiments (90T7663). The 1 : 2 adduct **19** is probably formed by an ene reaction of the 1,4-diene intermediate **16** to give **18**, followed by an intramolecular Diels–Alder reaction.

The reaction of 3-vinylbenzofuran with DMAD has also been studied; the corresponding dibenzofuran was obtained (91AJC1085).

### 3. Vinylpyrroles

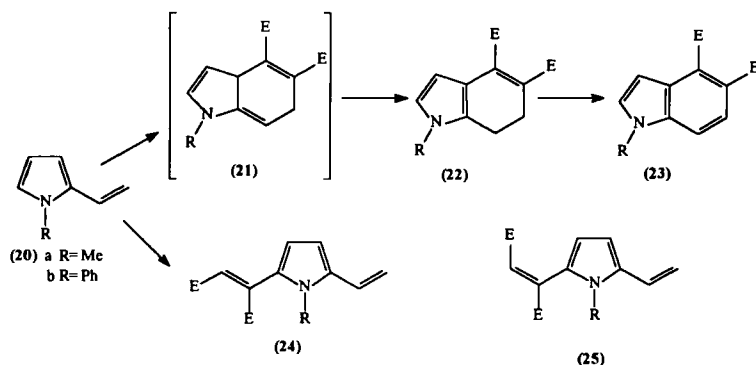
The synthesis of indoles from vinylpyrroles in reactions analogous to those of vinylfurans (43BSF163) and vinylthiophenes (53JA6329) was not studied until the 1980s, probably because of the inaccessibility and/or instability of the requisite vinylpyrroles [73JCS(P1)2450].



*N*-Methyl- and *N*-phenyl-2-vinylpyrroles **20a,b** react with DMAD at reflux temperature in chloroform to give, in moderate yields, the dihydroindoles **22** via a 1,3-H shift from the Diels–Alder intermediate **21** (55–75%) (80JOC4515). These adducts were readily converted into the corresponding indoles **23** with Dichlorodicyanoquinone (DDQ). 2-Vinylpyrrole failed to give [4+2]-cycloadducts with acetylenic esters (80JOC4515). Spectroscopic analysis of the product mixtures indicated the presence of polymeric compounds resulting from Michael addition reactions.

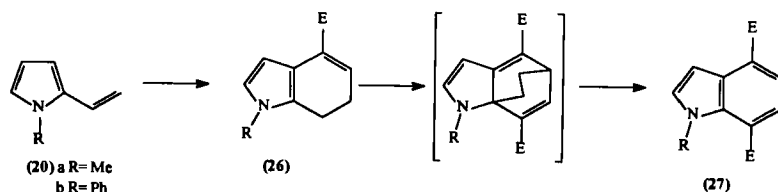
The reaction of 1-methyl-2-vinylpyrrole **20a** with DMAD was found to be temperature-dependent (81T1597). Thus, when the reaction was monitored at 20°C by NMR spectroscopy, it appeared that, although the dihydroindole **22a** (21%) was being formed directly from the vinylpyrrole, Michael addition of the acetylenic ester at the 5-position of the pyrrole ring also occurred to give maleic **24a** (20%) and fumaric **25a** (9%) ester derivatives. The assignment of the configuration of the Michael adducts was made on the basis of their  $^3J_{\text{CO,H}}$  coupling constants [84JCR(S)311].

In contrast to the change in reaction pathway for DMAD with 1-methyl-2-vinylpyrrole **20a** with temperature, 1-phenyl-2-vinylpyrrole **20b** was

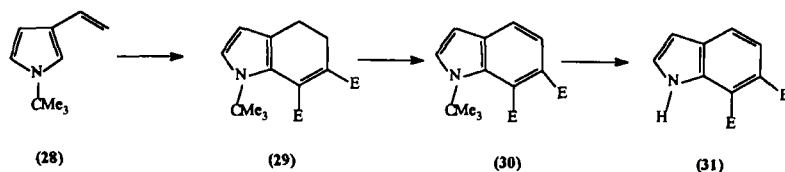


found to give [4+2]-cycloadducts exclusively over a temperature range from 20 to 80°C. The rate of the cycloaddition was, however, 5 times faster than the corresponding rate for the reaction of 1-methyl-2-vinylpyrrole under similar conditions (81T1597). In this work it was postulated that the phenyl group restrained the reactive diene in the cisoid conformation required for the cycloaddition and simultaneously hindered the Michael addition reaction at the 5-position of the pyrrole ring. To account for this possibility, a study of the reactivity of vinylpyrroles with substituents on the *N*-ring and 1-position of the vinylsubstituent was undertaken. The work confirmed that steric factors play an important role in the reactions of 2-vinylpyrroles with DMAD and no [4+2]-cycloadducts were obtained when both substituents R and R' were bulky [84JCS(P1)2541].

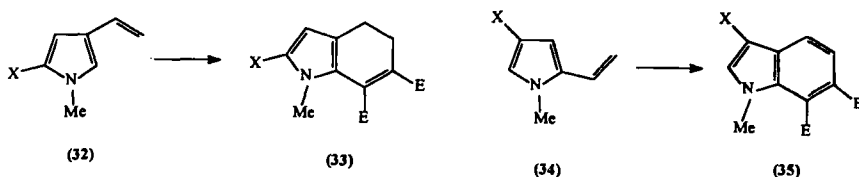
The reaction of MP with 1-methyl- and 1-phenyl-2-vinylpyrrole **20a,b** afforded 1-substituted indole-4,7-dicarboxylic esters **27** via a further [4+2]-cycloaddition to the initially formed 6,7-dihydroindole-4-carboxylic ester **26** by a second molecule of MP, followed by a retro-Diels–Alder extrusion of ethene (80JOC4515). Maximum yields were obtained with 2:1 ratio of MP to vinylpyrrole. The intermediate adduct **26** could not be isolated; and when the reaction was monitored by NMR spectroscopy, signals attributable to the dihydroindole-4-carboxylic ester **26** were of very low intensity, suggesting that the second and third steps of the reaction sequence were either comparable in rate or faster than the initial cycloaddition step.



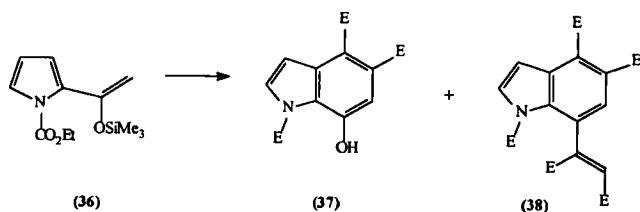
1-*tert*-Butyl-3-vinylpyrrole **28** reacted with DMAD in chloroform at reflux to give the corresponding dihydroindole **29**, which was also readily converted into indole **30** with DDQ (80JOC4515). In contrast to the stabilities of indole-4,5-dicarboxylic esters **23** obtained from 1-methyl- and 1-phenyl-2-vinylpyrroles, dimethyl 1-*tert*-butylindole-6,7-dicarboxylate **30** was thermally unstable, and distillation led to the complete extrusion of the *tert*-butyl group to give dimethyl indole-6,7-dicarboxylate **31**. The ease with which the de-*tert*-butylation occurs appears to result both from steric and electronic factors. In the indole diester **30**, the C7 ester group can conjugate with the pyrrole ring, thereby facilitating the loss of the *tert*-butyl group as 2-methylpropene. The effect is further enhanced by the buttressing effect of the two ester groups, which aid the removal of the proton from the *tert*-butyl group by the 7-carboxy substituent.



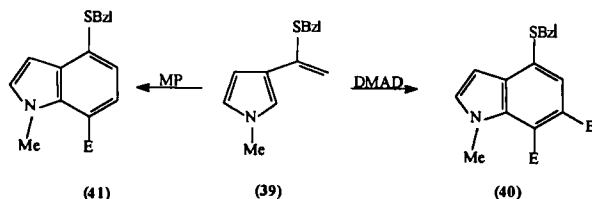
Cycloaddition reactions of 1-methyl-2-vinylpyrroles with substituents on the pyrrole ring have been used for the synthesis of 1-methylindoles that bear electron-withdrawing substituents at the 2- and 3-positions. The yields of the relatively more stable vinylpyrroles were generally lower than those obtained from simple 1- substituted 2- and 3-vinylpyrroles, and their reactivity was affected by the different positions of the electron-withdrawing groups (88SC1669). In all cases, the presence of these substituents inhibited the Michael addition reaction of DMAD to the pyrrole ring [81T1597; 84JCS(P1)2541]. The 4-vinylpyrroles **32**, possessing electron-withdrawing groups at the 2-position, required more vigorous reaction conditions to produce 4,5-dihydroindoles **33** than was needed for the corresponding formation of the 6,7-dihydroindoles **35** from the 4-substituted 2-vinylpyrroles **34**. These observations are consistent with the inhibiting cross-conjugative effect expected of an electron-withdrawing substituent at the 2-position on the concerted [4 + 2]-cycloaddition of the  $\pi$ -excessive system of the 4-vinylpyrroles with DMAD.



Substituted vinylpyrroles can be useful dienes for the synthesis of functionalized indoles. Silyl enol ether **36** reacted with DMAD in toluene under argon and afforded a mixture that was then exposed to air together with *p*-toluenesulfonic acid (91H1199). The hydroxyindole **37** was the minor cycloadduct (16%) and the major product (19%) was characterized as the 1:2 cycloadduct **38** [83H1933; 84JCR(S)218]. Interestingly, when the reaction was carried out without a solvent under an atmosphere of oxygen, the enhancement in the oxidative process led to the predominant formation of **37**. With this result, the reaction with MP was performed in the same manner and the regiospecific cycloadduct ethyl 7-hydroxyindole-1,4-dicarboxylate was obtained in 17% yield (91H1199).



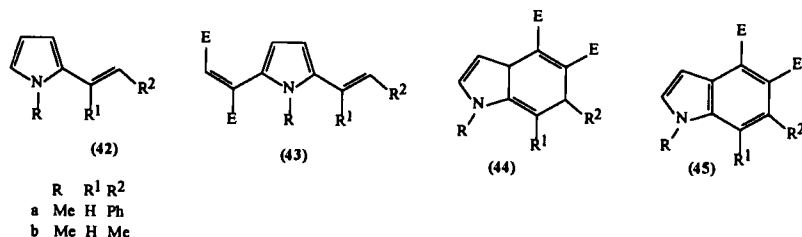
Sulfur-substituted 3-vinylpyrrole **39** generated *in situ* by alkylation of 3-thioacetyl-1-methylpyrrole has been used for the synthesis of indoles. In the reaction with DMAD, indole **40** was obtained in 30% yield. The reaction with MP afforded indole **41** with a low yield (10%) (91CPB489).



A phenyl group as a  $\beta$ -substituent on the vinyl group apparently increases the electron density of the 5-carbon of the pyrrole ring, so Michael-type addition is favored. The fumarate ester **43a** was obtained in 37% yield in the reaction of **42a** with DMAD (83JOC2488). With a methyl group as a  $\beta$ -substituent in **42b**, a mixture of the fumarate ester **43b** (37%) and the 3a,6-dihydroindole **44** (40%) was obtained (84MI1).

Vinylpyrroles **42** having electron-withdrawing substituents on the vinyl group are poor dienes for cycloaddition reactions with acetylenic esters. General reaction conditions such as heating at reflux in benzene or carbon

tetrachloride are not enough to force the reaction to take place. However, with a xylene or acetic acid/ether solvent or with a neat mixture of the reactants heated at reflux, the indoles **45** could be isolated in low yields (2–35%) (80JOC4582; 83JOC2488).



A final and interesting example of the use of vinylpyrroles as diene systems in Diels–Alder cycloadditions is the reaction of divinylporphyrins with DMAD and other activated dienophiles [*N*-phenylmaleimide (NPMI), Tetracyanoethylene (TCNE)], which provide a general route to bacterichlorin-like chromophores for the treatment of malignant tumors (86JOC1094; 91TL2875).

#### 4. Vinylindoles

The reaction of vinylindoles generated *in situ* with different dienophiles has been described as a route for the synthesis of carbazoles (59JA6010; 79JOC4402).

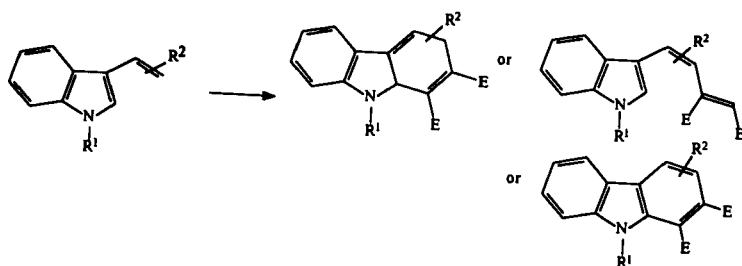
The reaction of vinylindoles with dienophiles has been used for the preparation of natural products and synthetic compounds with pharmacological interest because their substituted carbazole structures were more easily accessible by these cycloadditions than by other routes.

The reaction of functionalized 2- and 3-vinylindoles with different dienophiles has been extensively reviewed with special attention to stereochemistry (84T4837; 85C264, 85JHC585; 86CZ95; 88H1253).

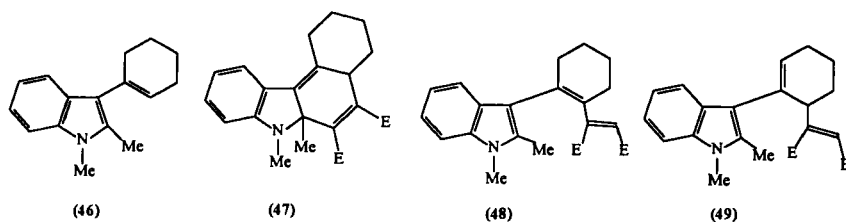
The cycloaddition reactions of 3-vinylindoles with acetylenic esters have been extensively studied. The reaction products generally obtained are [*b*]-annelated indoles, but Michael adducts can be isolated, depending on the substituents on the vinylindole (87HCA1419) (Scheme 1).

The reaction of vinylindoles containing the vinyl function incorporated in a carbocyclic ring provide access to novel polycyclic indole derivatives. The reaction of **46** with DMAD under forced conditions gave a mixture of Diels–Alder (**47**), Michael (**48**), and ene (**49**) adducts (91LA357).

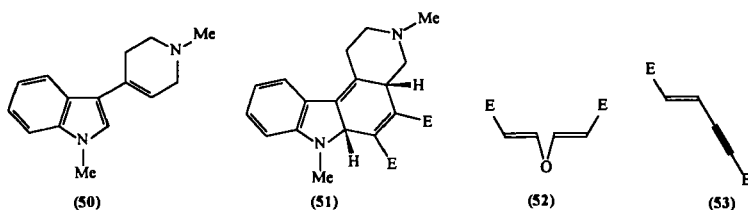
In this context, cycloaddition with 3-(1-methyl-1,2,3,6-tetrahydropyrid-4-yl)indoles of type **50** was studied with the purpose of establishing new



SCHEME 1



strategies for the synthesis of the pyrido[*c*]-annelated carbazole nucleus present in the highly active antitumoric ellipticines (91TL1771). The reaction with DMAD afforded the pyrido[*c*]-annelated carbazoles **51**, but the less reactive dienophile MP furnished primarily the unexpected simple alkene/alkyne derivatives **52** and **53**, obtained by dimerization of the MP and promoted by the amine function. Similar products have been detected previously as obtained from reactions of MP with tertiary amines (64CB1952).



Enol and thioenol ethers have been used as starting materials in a Diels–Alder reaction used as a key step for the synthesis of carbazomycins, which are newer carbazole alkaloids with antibiotic activity (87H325, 87TL3079; 89CPB1999; 92C441).

The reaction of the highly stable 1-substituted-3-(2-nitrovinyl) indoles with DMAD affords aromatic carbazoles by elimination of nitrous acid from the primary Diels–Alder cycloadduct (93JHC183).

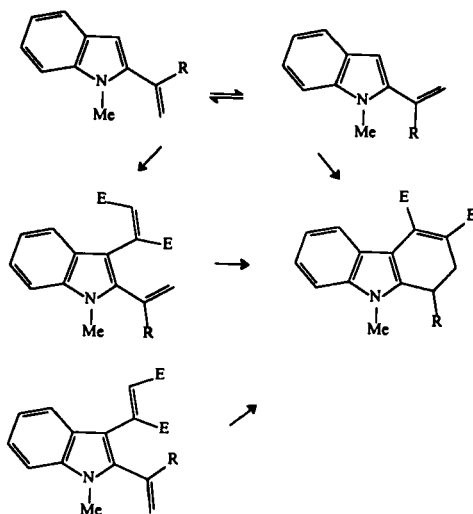


Neither the chemical reactivity of 2-vinylindoles nor its potential synthetic utility has been examined as extensively as that of the 3-isomers because access to these compounds is difficult (88HCA1060). These compounds have generally been synthesized by the standard Wittig reaction of the appropriate *N*-substituted 2-acylindole with methylenetriphenylphosphorane or via the reaction of *N*-substituted 2-indolyl lithium with a methyl ketone and subsequent elimination of a molecule of water from the carbinol intermediate (84T4837). The parent 2-vinylindole was prepared in 38% yield from (2-aminobenzyl)triphenylphosphonium bromide as a starting material by way of an intramolecular Wittig reaction (85T5313).

As a result of bond fixation within the indole system, the mesomeric interaction between the 2-vinyl group and the  $\pi$ -excessive heteroaromatic system is less than that for the 3-vinylindoles, and in the few reported reactions they have been shown to behave as dienophiles in [4+2]-cycloaddition reactions (81CC37).

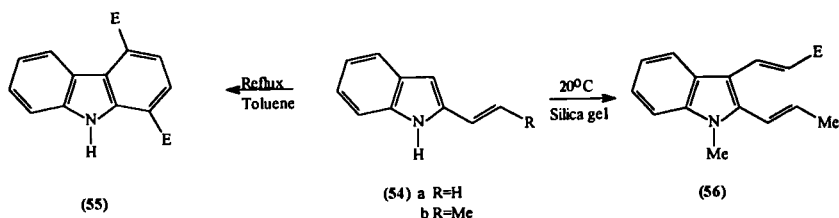
1-Methyl-2-vinylindole and 2-(1-methyl-2-indolyl)propene are both extremely labile compounds and dimerize readily through a reaction in which one molecule behaves as the dienophile and the other as the diene (71JOC1759). The reactivity of these compounds and other two 1'-substituted 1-(1-methyl-2-indolyl)ethenes ( $R = \text{Ph}$ , *tert*-butyl) was investigated in comparison with vinylpyrroles with DMAD as a dienophile (84T4837). Depending on the stability of the vinylindole and the steric hindrance between the *N*-methyl group on the indole ring and the 1'-substituent on the ethene moiety, cycloaddition competed with Michael addition and polymerization. It is noteworthy, however, that in all cases comparisons with the corresponding reactions of DMAD with 2-vinylpyrroles show the 2-vinylindoles to be approximately 10–100 times less reactive. No evidence was obtained for a Cope rearrangement of the Michael adducts to give tricyclic products, and when heated in the presence or absence of a solvent, adducts degenerated into polymeric material (Scheme 2).

The reaction of 2-vinylindole **54a** with MP (88H2353) in boiling toluene gave dimethyl carbazole-1,4-dicarboxylate **55** (8%) in a double Diels–Alder reaction with subsequent extrusion of ethene. This behavior was also observed in the reactions of 2-vinylpyrroles (80JOC4515) and 2- and 3-vinylthiophenes (85T2435; 87T269). Although reactions of 2-vinylindoles represent HOMO(diene)/LUMO(dienophile)-controlled processes according to the frontier molecular orbital (FMO) concept and the regiochemistry found for asymmetric olefinic dienophiles can be explained satisfactorily by a large–large/small–small interaction of the FMO coefficients, the reaction of 2-vinylindole with MP followed a reversed direction of addition.



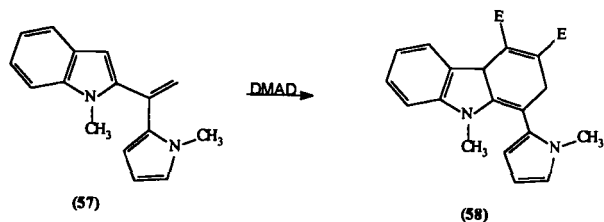
SCHEME 2

Different results were obtained when the vinylindole **54b**, dissolved in the liquid dienophile (MP), was treated with a 20-fold (by weight) amount of activated silica gel 60 and the mixture was allowed to stand at room temperature for 3 days. In this case the reaction with the alkyne proceeded with regio- and stereoselectivity to give the Michael adduct **56** (90JOC5368).



An interesting reactivity comparison was carried out with 1-(1-methyl-2-indolyl)-1-(*N*-methyl-2'-pyrrolyl)ethene **57** obtained via the corresponding carbinol. An inspection of its structure suggests that the molecule could react in a cycloaddition reaction as a vinylindole or as a 2-vinylpyrrole. In reactions with dienophiles, which include DMAD, it reacted as a 2-vinylindole, affording a carbazole derivative **58** (89JHC1869).

Other reactions of 2-vinylindoles with DMAD found in the literature are the reaction of *N*-benzyl-2-vinylindole, reported as a proof of structure of carbazoles obtained by the Fischer indole synthesis (82CJC419); the reaction of  $\beta$ -aryl-2-vinylindoles, reported as a synthetic route to poten-

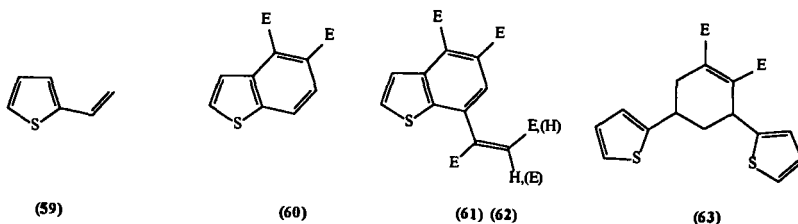


tial DNA binders quinolono[4,3-*b*]- and -[3,4-*b*]carbazoles (93TL1347); and the reaction of 2-vinylindole to give the corresponding dihydrocarbazole, formed by a 1,3-H shift from the primarily formed cycloadduct (88HCA1060; 90JOC5368).

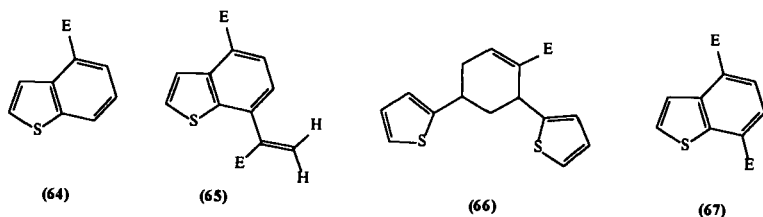
### 5. Vinylthiophenes

The reaction of vinylthiophenes with acetylenic esters has been studied in detail. Although the overall yields were not generally good, structure determinations were carried out even on minor compounds obtained in very low yield.

The reaction of 2-vinylthiophene **59** with DMAD in benzene at reflux afforded four compounds: **60**–**63**. (85T2435). Compound **60** was the result of a Diels–Alder cycloaddition followed by aromatization. The adducts **61** and **62** are obtained by an ene reaction. The structure of compound **63** was unique for cycloadditions of vinyl heterocycles.

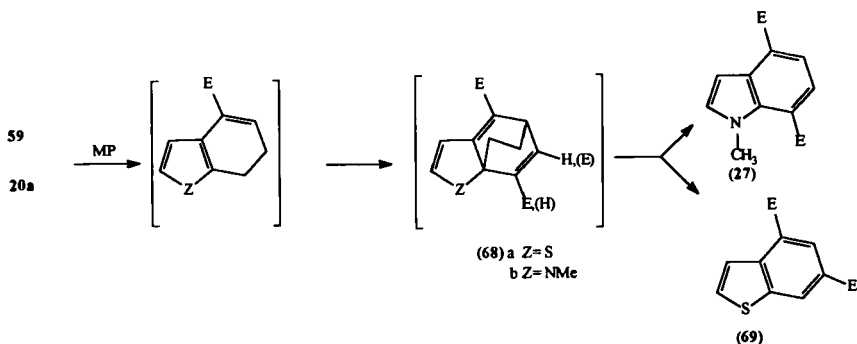


The reaction between the less reactive dienophile MP and 2-vinylthiophene **59** in  $\text{CH}_2\text{Cl}_2$  was conducted at  $100^\circ\text{C}$  under pressure and four compounds, **64**, **65**, **66**, and **67**, could be isolated and characterized spectroscopically (85T2435). The adduct **67** is the result of a second addition of MP to the normal cycloadduct, followed by Diels–Alder elimination of ethylene in a way similar to that reported for *N*-substituted 2-vinylpyrroles (Section II,A,3) (80JOC4515). It is useful to point out the structure of adducts **61**, **62**, and **65** because the ene reaction of thiophene compounds is not a common one (75TL4471).



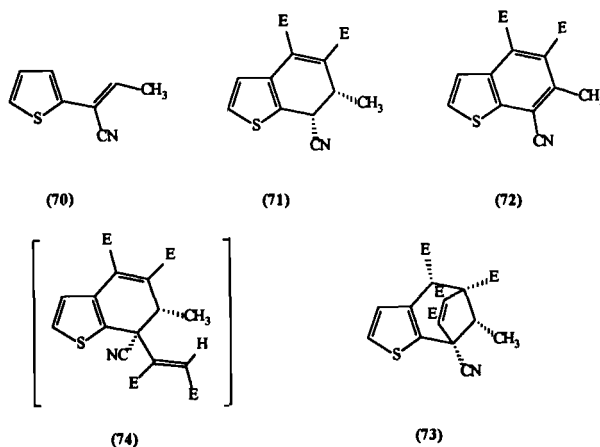
The results of this reaction changed when the conditions were slightly different. Other authors have reported that with MP in refluxing benzene for 2 days, the polymerization of 2-vinylthiophene **59** took place quite rapidly and no adducts could be isolated (89JHC397). However, when a neat 1 : 3 mixture of **59** and MP was heated in a sealed tube at 110° for 4 days, compound **69** was isolated in 70% yield. One of the striking contrasts of this reaction, in comparison with the addition of MP to 1-methyl-2-vinylpyrrole **20a**, is the different regioselectivity of the reaction between the disymmetric dienophile MP with the nonisolated intermediates. In this latter case the indole **27** was isolated.

The key factor that accounts for differences in regioselectivity between the thiophene and the pyrrole is probably the greater mesomeric release of electrons from the nitrogen atom through the double bonds (89JHC397).

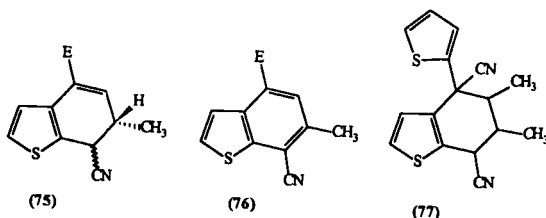


The presence of substituents in the vinyl group of vinylthiophenes modifies reactivity. The vinylthiophene **70**, obtained via a Knoevenagel condensation from 2-thienylacetonitrile and acetaldehyde as an 87 : 13 *E*-*Z* mixture, reacted with DMAD (11 days at reflux in acetonitrile) to give the adducts **71**, **72**, and **73** (87T991). The surprising compound **73** could be formed through the ene intermediate **74**.

The reaction of vinylthiophene **70** with MP (15 days) gave two adducts in very low yield: **75** (1%) and **76** (3%). The reaction was accompanied by polymer formation, and a mixture of diastereomeric dimers of vinylthio-



phene **77** (5.5%) could also be isolated and characterized spectroscopically (87T991).

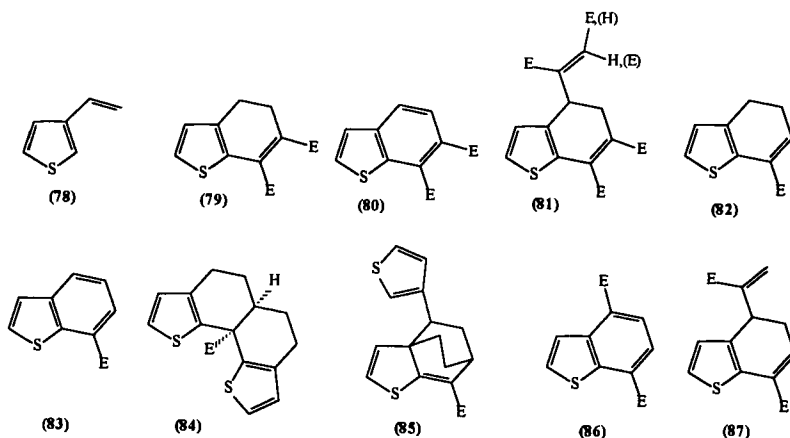


Dimethyl acetylenedicarboxylate reacted slowly with 3-vinylthiophene **78** to give a mixture of two major products, **79** and **80**. A small amount of a mixture, which could be the *Z* and *E* ethenedioates **81**, was formed by ene addition to the initial Diels–Alder cycloadduct (87T269).

Reaction with MP afforded the adducts **82**, **83**, **84**, **85**, **86**, and **87**. The adducts **84** and **85** are the result of a further reaction of the normal Diels–Alder adduct **82** with a second molecule of 3-vinylthiophene, which behave as diene and dienophile, respectively (87T269).

## 6. Vinylbenzothiophenes

Vinylbenzothiophenes also react with acetylenic compounds as diene systems in reactions reported in the literature. One example is the reaction of 2-vinylbenzo[*b*]thiophene with DMAD and with dibenzoylacetylene, affording the corresponding Diels–Alder cycloadducts [89IJC(B)724].

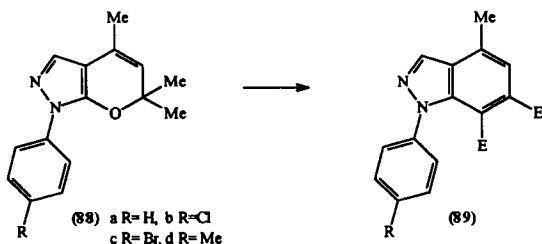


## 7. Vinylpyrazoles

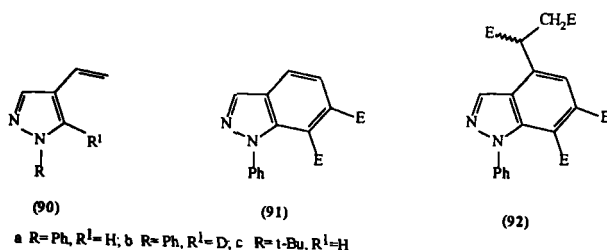
Several examples in which pyrazole fails to undergo cycloaddition reactions under conditions similar to those in which other heterocyclic compounds react have been reported in the literature (84MI2).

Although in theory vinylpyrazoles can react with dienophiles to give Diels–Alder adducts, the reaction destroys the “aromaticity” of the pyrazole ring, and these dienic systems show a very low reactivity toward dienophiles.

The reaction of 1-aryl-4,6,6-trimethyl-3-phenyl-1,6-dihydropyrano[2,3-*c*]pyrazoles **88a–d** with DMAD in dimethylformamide (DMF) at reflux is the first example of a Diels–Alder reaction involving the pyrazole ring. The reaction afforded an indazole **89** by elimination of a molecule of acetone from the intermediate cycloadduct (83S852). The *s-cis* conformation of the reactive diene fixed by the dihydropyran and the aromatization process to afford the indazole by elimination of acetone could be the driving force for this reaction.

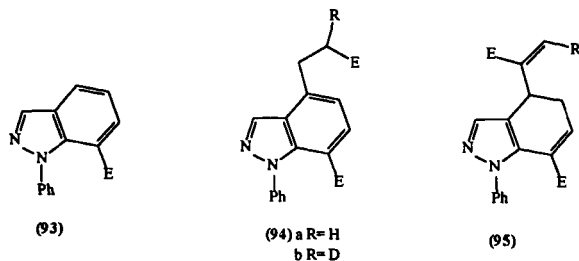


In comparison with the unstable and reactive vinylpyrroles and vinylindoles, 1-phenyl-4-vinylpyrazole **90a** is a very stable and unreactive compound, which was recovered unchanged even after 24-hour reflux with DMAD in  $\text{CH}_2\text{Cl}_2$ . Only when the reaction was conducted in  $\text{CH}_2\text{Cl}_2$  at  $150^\circ$  for 14 hours under pressure of 8–10 atm in a steel bomb did the reaction take place to afford indazole **91**, which was isolated in 18% yield along with a large proportion of polymeric material [85JCR(S)84]. In the absence of solvent, the major reaction product was the 2:1 adduct **92**, resulting from a further ene reaction of the primary Diels–Alder adduct with a second molecule of DMAD followed by two [1,3]-sigmatropic hydrogen shifts.



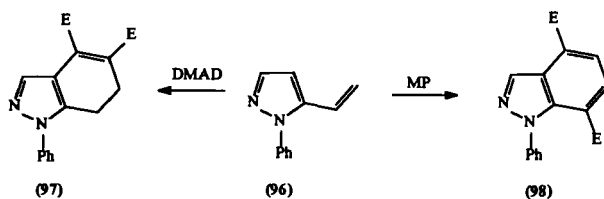
The reaction of 1-phenyl-4-vinylpyrazole **90a** with the less reactive dienophile MP was conducted at  $150^\circ$  under pressure for 5 days, affording the indazole **93** and a mixture of isomers **94a** and **95a** (86T6683). These 1:2 adducts were obtained by a Diels–Alder cycloaddition followed by a nonregioselective ene reaction.

As the mixture of adducts **94** and **95** could not be resolved chromatographically and the NMR study did not allow a clear assignment of the signals, the same reaction was studied using the deuterated pyrazole **90b** as starting material (90M81). The presence of deuterium in the new adducts **94b** and **95b** allowed the unequivocal assignment of NMR signals and confirmed that the mechanism of the ene reaction was a concerted *cis* process via a six-membered transition state.



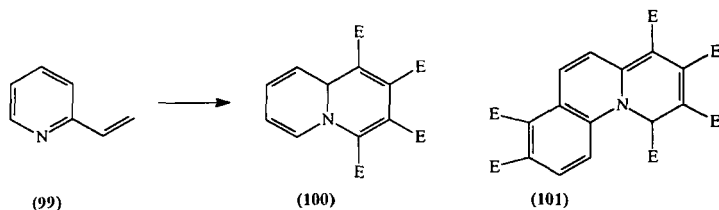
To see if the presence of substituents either on the pyrazole ring or the vinyl group favorably modified the yield of the cycloadducts, the reactivity of other alkenylpyrazoles toward dienophiles was studied (89M1113). The reaction of 1-*tert*-butyl-4-vinylpyrazole **90c** with DMAD occurred in a manner similar to the reaction of 1-phenyl-4-vinylpyrazole **90a**; however, the isolated dihydroindazole was stable and did not convert into the corresponding aromatized indazole. In the reaction with MP only a Diels–Alder adduct was obtained, and no traces of 1:2 adducts could be detected. These results showed that the capacity of vinylpyrazoles to participate in cycloaddition reactions was not limited to one kind of substituent on the nitrogen ring. The scope of this reaction is limited, however, and the reaction failed with small changes by substitution on the vinyl group.

1-Phenyl-5-vinylpyrazole **96** also behaves as a diene in reactions with DMAD and MP [90JCS(P)2749], but the reactivity in such cycloadditions was lower, with reaction times much longer than those required for 1-phenyl-4-vinylpyrazole. In the reaction with DMAD the dihydroindazole **97** was isolated, and with MP the obtained indazole **98** was the result of a double Diels–Alder reaction, followed by extrusion of ethene, as has been reported for vinylpyrroles and vinylthiophenes (80JOC4515; 87T269).



## 8. Vinylpyridines

2-Vinylpyridine **99** reacted with DMAD to afford the 2:1 adducts **100** and **101** [68JCS(C)387].

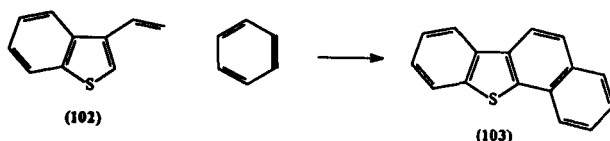




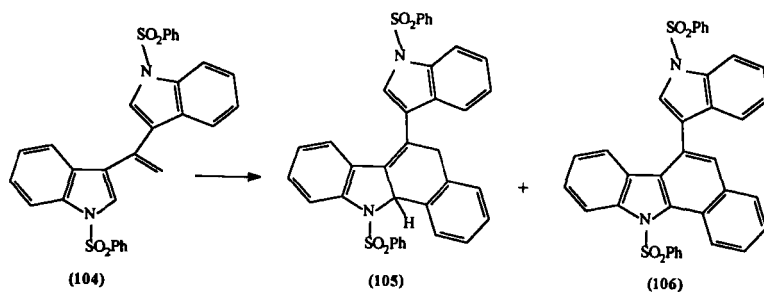
## B. REACTIONS WITH ARYNES

The very reactive arynes have also been used as dienophiles in Diels–Alder cycloadditions with vinyl heterocycles and are included here, after the acetylenic esters, because of the similarity of their reactive functions. This reaction is of considerable importance because of its application in the synthesis of polycyclic compounds.

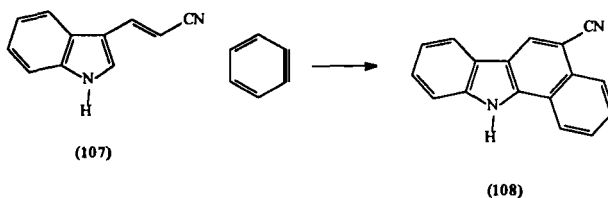
One example is the reaction with benzyne of 3-vinylbenzo[*b*]thiophene **102**, prepared by dehydration of 2-(3-benzo[*b*]thienyl)ethanol, to give 11-thiabenzob[*a*]fluorene **103** (65AJC1781).



1,1-Bis(3-indolyl)ethenes **104** also reacted as a  $4\pi$ -electron system with benzyne to give Diels–Alder cycloadducts **105** and **106**. The reaction involve the olefinic double bond and represents a strategy for the synthesis of functionalized carbazole derivatives (86C124).



In a similar reaction (*E*)-3-(indo-3-yl)propenenitrile **107** afforded 11*H*-5-cyanobenzo[*a*]carbazole **108** (82T3019; 86CZ95).



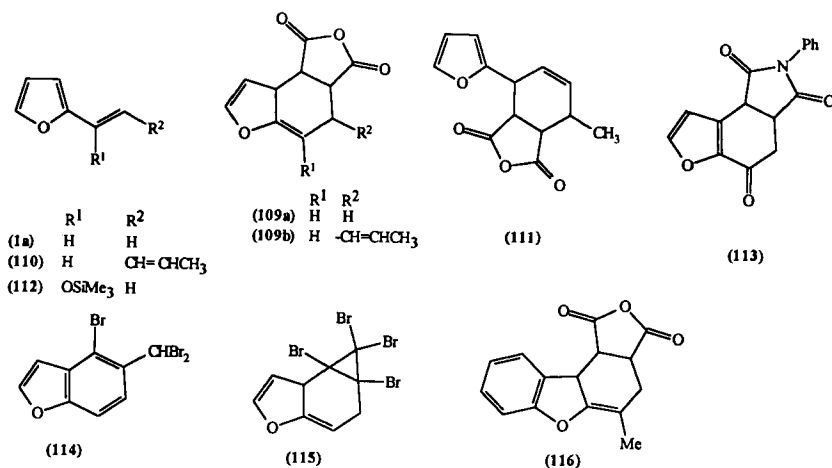
## C. REACTIONS WITH CYCLIC OLEFINS

## 1. Vinylfurans

In contrast with the reactions with acetylenic esters (see Section II,A,1), 2-vinylfuran **1a** reacts with maleic anhydride (MA) exclusively through the endo-exo diene system to afford the 3a,4,5,6-tetrahydrobenzofuran-4,5-dicarboxylic acid anhydride **109a** with 79% yield (43BSF163). This work was extended to 2-furypolyenes, and 1-(2'-furyl)-1,3-pentadiene **110** gave adduct **109b** and isomeric compound **111** (53N581). In all the reactions studied, the conjugated system made up the exocyclic double bond and the adjacent furan ring bond proved to be more reactive toward MA than the furan ring itself. However, electron-withdrawing substituents on the vinyl group modify the reactivity of the diene, preventing such cycloaddition. Thus 2-furylacrolein, 3-(2'-furyl)acrylic acid, and 2-( $\beta$ -nitrovinyl)furan do not act as dienes at temperatures below 100°C (46JA2732).

The 2-(1-trimethylsilyloxyvinyl)furan **112** reacts with *N*-phenylmaleimide (NPMI) also through the exocyclic diene to afford a 1 : 1 cycloadduct which was rearomatized by air oxidation to give compound **113** (83H1933).

Diels-Alder reaction of 2-vinylfuran with tetrabromocyclopropene gave functionalized benzofuran **114** by selective cleavage of the C1/C3 bond of intermediate **115** (90TL4581).



## 2. Vinylbenzofurans

Isopropenylbenzofuran **15** readily added to MA to form an adduct for which structure **116** was initially assigned and later confirmed by spectroscopic analysis (70AJC2119).

3-Vinylbenzofuran gave the expected [4+2]-adducts with MA and NPMI. The anhydride derivative was hydrolyzed to the corresponding dicarboxylic acid by water in acetone, while in the presence of mineral acid double-bond rearrangement to the more aromatic acid accompanied hydrolysis. Under mildly acidic conditions the adduct from NPMI rearranged to its more aromatic isomer (91AJC1085). 3-Vinylbenzofuran reacted also with 1,4-naphthoquinone to give the primary Diels–Alder cycloadduct together with traces of dehydrogenation products (91-AJC907).

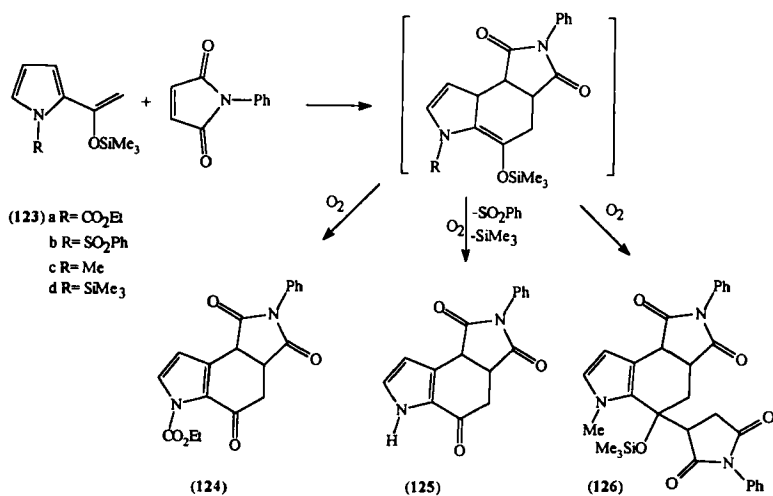
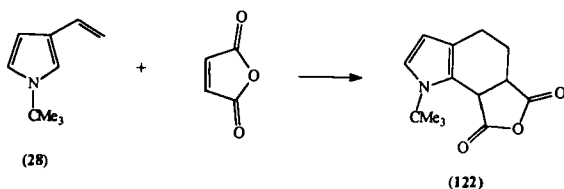
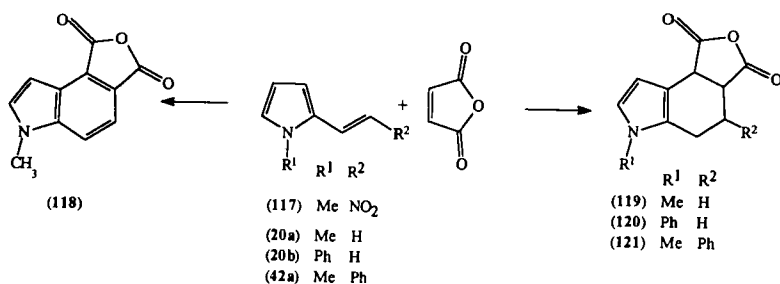
### 3. Vinylpyrroles

The first vinylpyrroles studied as diene systems in Diels–Alder reactions were the  $\beta$ -nitrovinyl-*N*-methylpyrroles because they are stable and readily available from condensation of the corresponding carboxaldehydes with nitromethane. The  $\beta$ -nitrovinylpyrrole **117** added to MA and yielded the corresponding *N*-methylindole-4,5-dicarboxylic anhydride **118**. The process is believed to follow the normal Diels–Alder [4+2]-cycloaddition pathway, with subsequent loss of nitrous acid to give the fully aromatized adduct [73JCS(P1)2450].

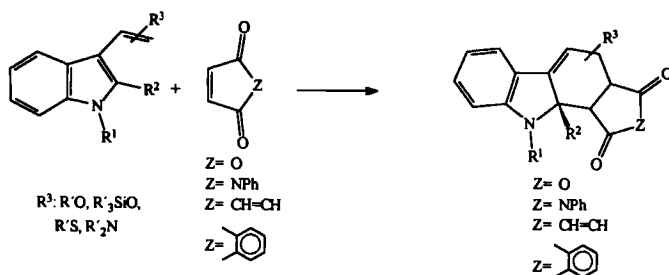
1-Methyl- or 1-phenyl-2-vinyl-1*H*-pyrroles **20a** and **20b** and 1-*tert*-butyl-3-vinylpyrrole **28** react with MA to give initially tetrahydroindole derivatives **119**, **120**, and **122**, respectively, with good yields (54–75%) (80JOC4515). The reactions were extremely rapid at room temperature in chloroform and in benzene. The rate constants were measured for the cycloaddition reaction of 1-methyl-2-vinylpyrrole, being 5000 times faster with MA than with DMAD at room temperature. Conversely, vinylpyrrole **42a** was a poor diene and reacted with MA only under forcing conditions to give the [4+2]-adduct **121** with 37% yield. It is interesting to point out that furan and thiophene counterparts did not react at all, and this difference in reactivity among the vinyl derivatives of monoheterocycles is explained by the authors in terms of the greater electron-releasing ability of the nitrogen atom in the pyrrole (83JOC2488).

*N*-Tosyl-2-vinylpyrrole adds to tetrabromocyclopropane to give halogenated indoles (see Section II,C,1) (90TL4581).

Silyl enol ethers of *N*-substituted 2-acetylpyrroles **123a–d** provide indole skeletons through a [4+2]-cycloaddition with NPMI. The above reaction occurred with diverse rearomatization processes, depending on the *N*-substituent: air oxidation (*N*-ethoxycarbonyl), elimination of PhSO<sub>2</sub> and Me<sub>3</sub>Si groups (*N*-phenylsulfonyl), or ene reaction with a further molecule of dienophile (*N*-methyl) to afford, respectively, the indole derivatives **124–126** (90TL4613).



Sulfur-substituted 3-vinylpyrroles generated from *N*-methyl-3-thioacetylpyrrole have been used to accomplish the synthesis of functionalized indoles by Diels–Alder cycloaddition. In the reactions with MA, NPMI, and naphthoquinone the [4 + 2]-cycloadducts were obtained with low to moderate yields and directly transformed to the corresponding indoles by treatment with DDQ (91CPB489).

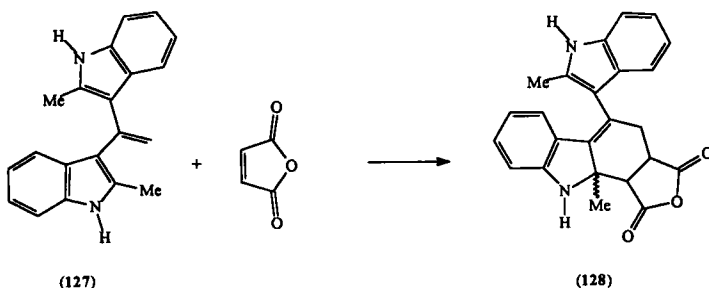


SCHEME 3

#### 4. Vinylindoles

The reactivity toward NPMI, MA, and quinones of 3-vinylindoles (78AJC1841; 81AJC1483; 88HCA467; 90TL1551; 92MI1; 93JHC81) as well as the substituted derivatives on the diene system with alkoxy, alkylthio, amido, and amino groups (86LA2065; 89CPB1999; 91CPB489; 92JOC910) or with the vinyl function incorporated into a ring (68HCA264; 91HCA430; 91LA357; 91TL1771) has been widely studied. 3-Alkenylindoles are efficient  $4\pi$ -components in Diels–Alder reactions, and they constitute versatile substrates for the regio- and stereoselectively controlled syntheses of indole derivatives. Primary Diels–Alder cycloadducts, tetrahydrocarbazoles (derived from the former via a formal 1,3-H shift) or fully aromatized carbazole derivatives can be isolated. Moderate to good yields were obtained under thermal conditions, but in some cases, such as the 1'-phenyl-substituted 3-vinylindoles, reaction only occurs sufficiently rapidly with NPMI in the presence of a Lewis acid (Scheme 3) (87C126).

Usually the  $[4+2]$ -cycloadditions were stereospecific and afforded 1 : 1 endo-adducts. However an endo–exo mixture of cycloadduct **128** was isolated from the reaction of 1,1-bis(3-indolyl)ethene **127** and MA (86C124).



Regioselectivity in the reaction of (*E*)-2'-methoxy-1-benzenesulfonyl-3-vinylindole with asymmetric 1,4-benzoquinones has been studied. Al-

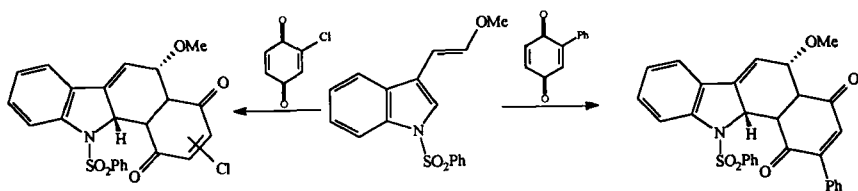
though the Diels–Alder reaction with 2-phenyl-1,4-benzoquinone took place regioselectively, probably as a result of steric factors, the analogous reaction with the chloro-substituted carbodienophile did not, giving rise to a 1 : 1 mixture of regioisomers instead. On the other hand, the (*Z*)-isomer did not react with benzoquinone dienophiles to furnish any cycloadducts (92JOC910). (Scheme 4)

$\beta$ -Nitrovinylindoles **129** react with NPMI and 1,4-quinones in refluxing acetic acid to yield carbazole derivatives **130–133**; but in the case of NPMI, the use of other solvents such as dimethyl sulfoxide, pyridine, or ethanol produced the bridged carbazoles **134** and **135**. Even in hydrochloric acid/ethanol these 1 : 2 adducts were obtained as major products. Hence, the role of acetic acid is still unknown (74IJC493; 93JHC183). An analogous reaction take place between 3-(2-methoxyvinyl)-1-phenylsulfonylindole and NPMI to afford an endo–cisoid–endo bridged carbazole (87HCA1419). The following mechanism was proposed in both cases to explain their formation: The initial Diels–Alder adducts eliminate nitrous acid or methanol, and the intermediate adduct then undergoes a further cycloaddition with NPMI to produce the corresponding 1 : 2 cycloadduct.

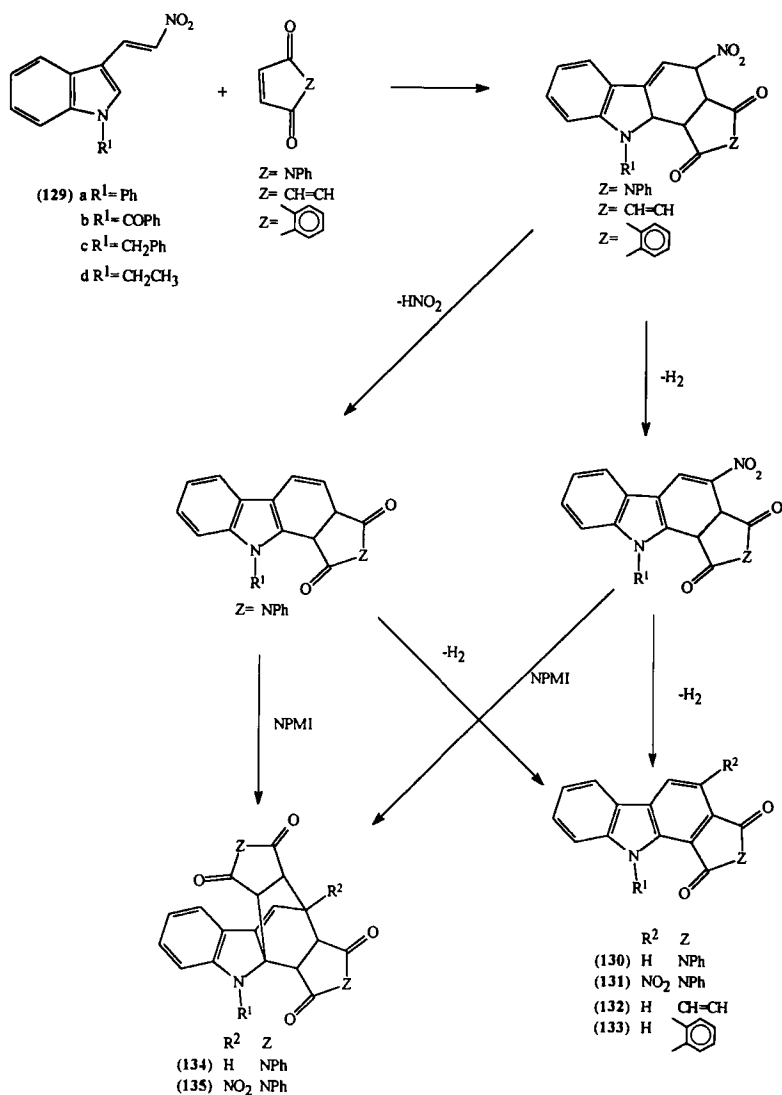
Tetrahydrocarbazoles could be prepared in one-flask syntheses from indoles, ketones, or aldehydes and maleimides with acid catalysis. The reactions involve a condensation of the indole with the ketone or aldehyde followed by *in situ* trapping of the vinylindole in a Diels–Alder addition with maleimide (93JHC81).

Ene reaction or dimerization competed with the Diels–Alder cycloaddition when 3-(2-propenyl) *N*-substituted indoles **136** were employed as diene systems toward NPMI (88HCA467). On the other hand, with  $\beta$ -substituted 3-vinyl-1*H*-indoles **137** and the same dienophile, the products include carbazole derivatives and Michael adducts (Scheme 5) (87HCA1419).

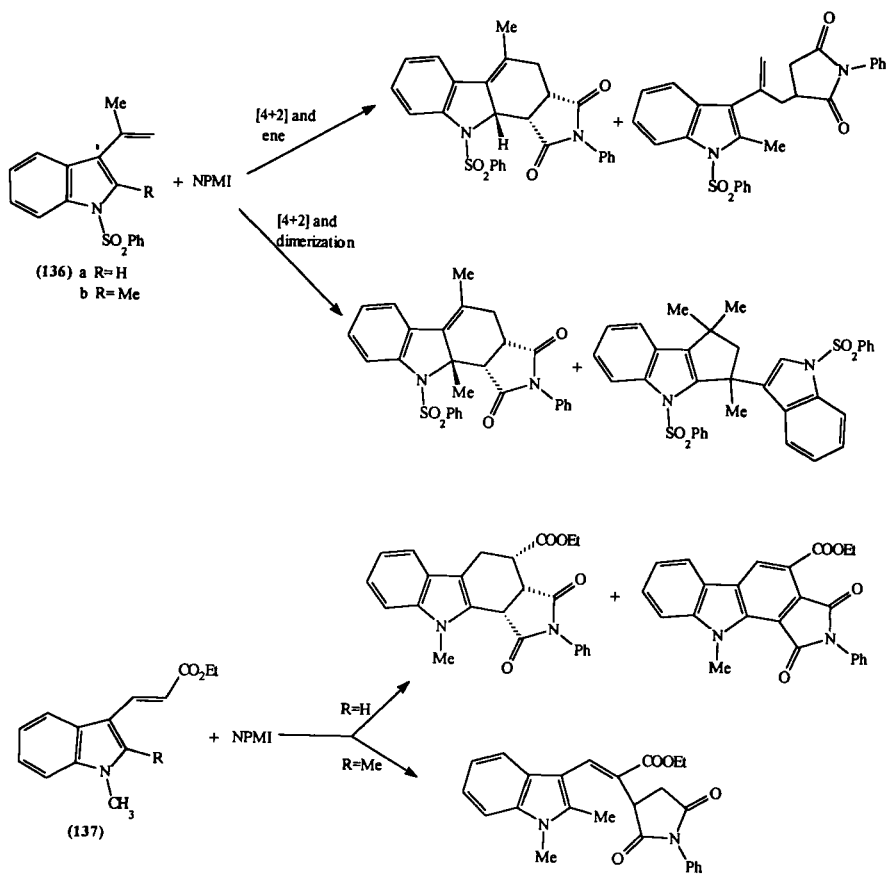
2-Vinylindoles are also efficient  $4\pi$ -components in cycloaddition reactions and provide the corresponding [*c*]-annulated carbazoles which react, for example, with NPMI, MA, and quinones [82CJC419; 83IJC(B)1004; 88HCA1060] (Scheme 6). Although in the more usual cases the result of



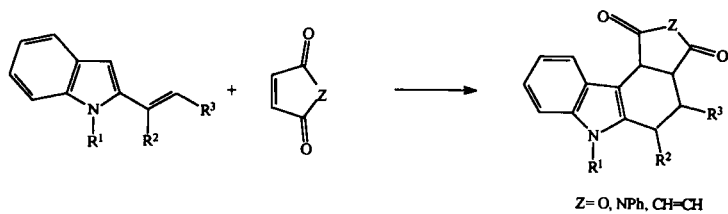
SCHEME 4



the cycloaddition can be explained by a concerted mechanism on the basis of FMO theory as a HOMO(diene)/LUMO(dienophile)-controlled process for highly polarized 2-alkenylindoles, a stepwise process has been proposed to explain the outcome of their reactions (90JOC5368).



SCHEME 5



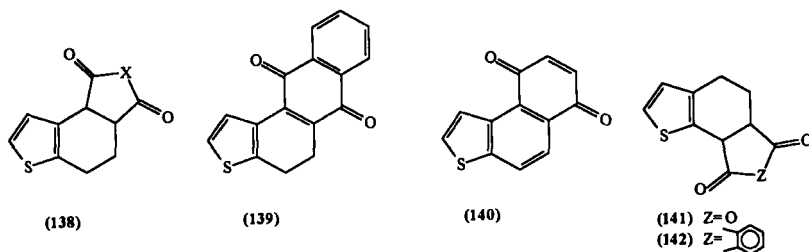
SCHEME 6



## 5. Vinylthiophenes

2-Vinylthiophene **59** and 3-vinylthiophene **78** behave as moderately active dienes with MA, giving fair yields of the corresponding 1 : 1 cycloadducts **138** and **141** (53JA6329; 57JCS4958; 87T269). In the former case, the yield decreased when the reaction time was prolonged due to copolymerization. Dioxoanthra[*b*]thiophenes **139** and **142** could be obtained using the Diels–Alder cycloaddition reaction of 1,4-naphthoquinone with 2- or 3-vinylthiophene (81JHC967). Also, 2-vinylthiophene reacted slowly with 1,4-benzoquinone to give a 43% yield of the fully aromatized naphthothio-*phene* derivative **140**; and so far, it has not proved possible to isolate an adduct that has not undergone dehydrogenation by excess quinone (57JCS4958).

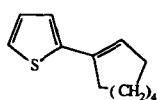
Diels–Alder reaction of 2-vinylthiophene with tetrabromocyclopropene gave functionalized benzothiophene by selective cleavage of the initial cycloadduct (Section II,C,1) (90TL4581).



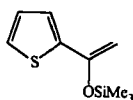
Derivatives with substituents on the vinyl group, such as thienylcycloalkenes **143**, the 2-(1-cyanoallyl)thiophene **71**, or 2-(1-trimethylsilyloxyvinyl)thiophene **144**, have also been reported as 4 $\pi$ -components in Diels–Alder reactions with MA and NPMI. Addition of maleic anhydride to 1-(2-thienyl)cyclohex-1-ene **143a** and 1-(2-thienyl)cyclohept-1-ene **143b** afforded bis adducts; these structures were not given by the authors, but reaction with 1-(2-thienyl)cyclooct-1-ene **143c** produced the normal monoadduct **145** (50JA571). On the other hand, 2-(1-cyanoallyl)thiophene **71** reacted slowly with NPMI to give a mixture of the epimers **146** and **147** whose formation could be explained as result of Diels–Alder cycloaddition followed by a nonstereoselective 1,3-migration of hydrogen that rearomatizes the thiophene ring (87T991).

The 2-(1-trimethylsilyloxyvinyl)thiophene **144** showed the same chemical behavior, acting as a diene with a typical dienophile such as NPMI;

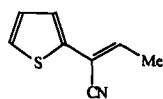
it is interesting to point out, however, that the relative rate was 6 times faster than that for analogous furan, despite the more aromatic character of the thiophene. Thus the thiophene derivative preserved Diels–Alder reactivity better than the furan—a fact that was explained according to FMO theory by considering the major contribution to be a HOMO(diene)/LUMO(dienophile) interaction and by recognizing that the energy of the HOMO and the size of the HOMO coefficient at the end of the silyloxyvinyl group are higher in the thiophene than in the furan (83H1933).



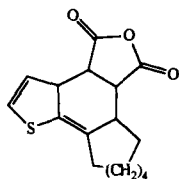
(143) a  $n=2$   
b  $n=3$   
c  $n=4$



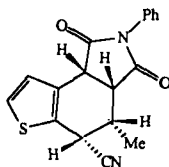
(144)



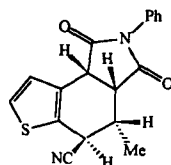
(71)



(145)



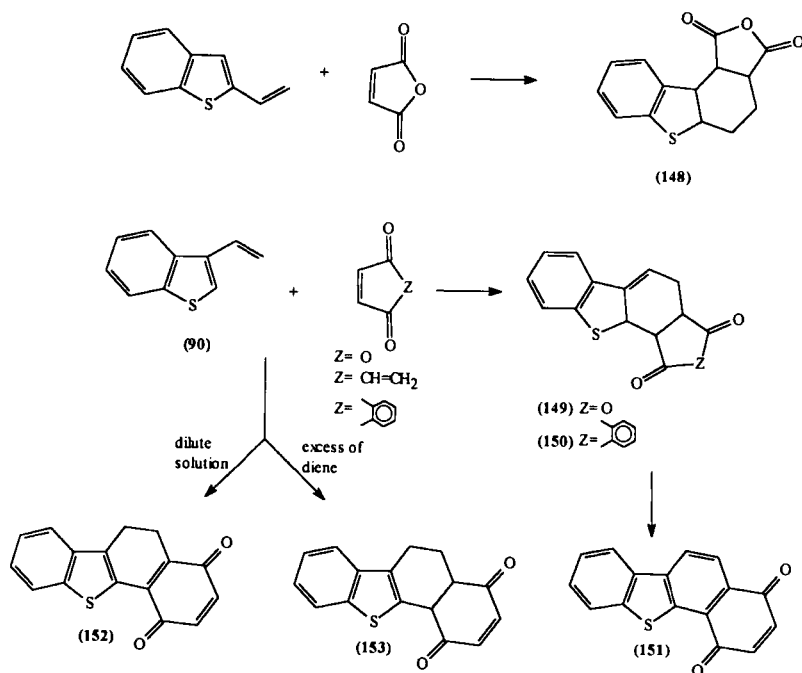
(146)



(147)

## 6. Vinylbenzothiophenes

Maleic anhydride and quinones underwent [4 + 2]-cycloadditions with 2- and 3-vinylbenzo[*b*]thiophenes to afford in good yield the corresponding annulated heterocycles **148–150** [57JCS3366, 57JCS4961; 89IJC(B)724]. 3-Vinylbenzo[*b*]thiophene **90** reacted with benzoquinone to give a fully aromatized 1 : 1 cycloadduct **151** as result of a Diels–Alder reaction followed by dehydrogenation by excess quinone. Isolation of a dihydro derivative **152** was possible using a weaker solution of 3-vinylbenzo[*b*]thiophene, whereas a further excess of the vinyl compound and a very short reaction time afforded the tetrahydro derivative **153** (79AJC145). On the other hand, primary Diels–Alder adducts are isolated from 1-(3-benzo[*b*]thiophene)cyclohex-1-ene and 1-(3-benzo[*b*]thiophene)-3,4-dihydronaphthalene on reaction with MA (50JA571).

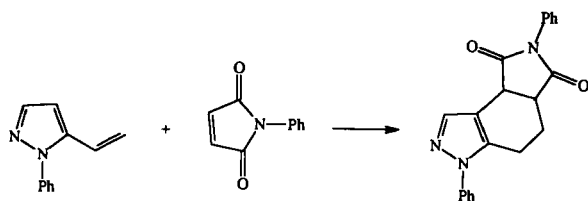
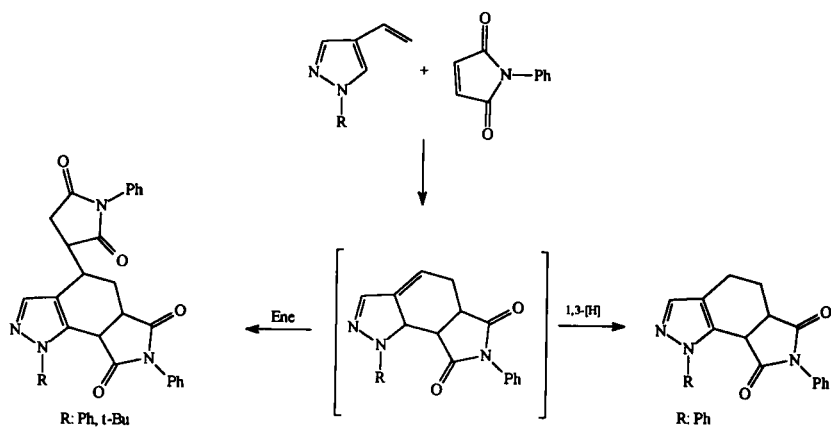


## 7. Vinylpyrazoles

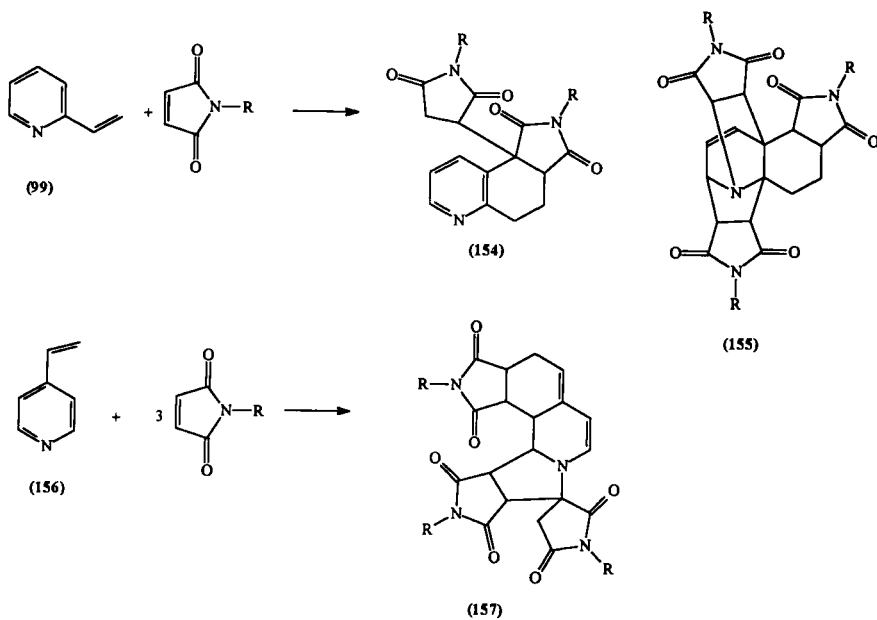
Vinylpyrazoles react with NPMI to afford functionalized indazole derivatives through [4 + 2]-cycloaddition reactions in a way similar to that of other carbodienophiles such as acetylenic esters. So with 4-vinylpyrazole derivatives, mixtures of 1:1 and 1:2 cycloadducts (formed via an ene reaction) were obtained (86T6683; 89M1113), whereas with the 5-isomer only the 1:1 cycloadduct was isolated (Scheme 7) [90JCS(P1)2749].

## 8. Vinylpyridines

Vinylpyridines add to *N*-alkyl- or phenyl-substituted maleimides to give unexpected 1:2 and 1:3 adducts. From the reaction of 2-vinylpyridine **99** with *N*-alkylmaleimides the 1:2 addition products **154**, which are tetrahydroquinoline derivatives, could be isolated in the presence of polymerization inhibitors. Furthermore, 1:3 adducts **155** are formed, representing an unusual type of cycloaddition involving the pyridine ring. On the other hand, 4-vinylpyridine **156** combines with 3 moles of dienophilic *N*-alkylmaleimides in the presence of polymerization inhibitors to afford the spiro compounds **157** (73HCA440).



SCHEME 7

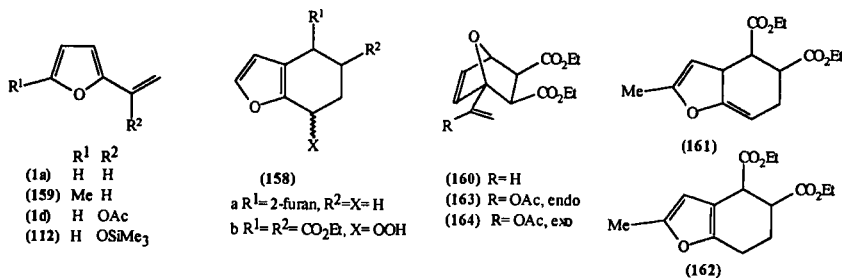


## D. REACTIONS WITH ACYCLIC OLEFINS

## 1. Vinylfurans

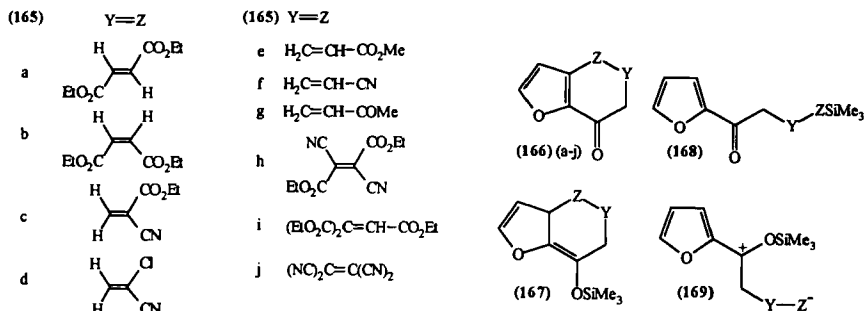
2-Vinylfuran **1a** undergoes thermal dimerization. The dimer **158a** is formed by a Diels–Alder reaction in which 1 mole of **1a** acts as diene and another as acyclic olefin dienophile, followed by isomerization (65BCJ675).

The vinylfuran **1a** does not react with dimethyl maleate at reflux in toluene, but this compound and other vinylfurans **1d** and **159** gave reactions with dimethyl maleate very nicely at high pressure (15 kbar and 30°C in dichloromethane) (81JOC5454). Nevertheless, remarkable differences were found among the different substrates. Thus **1a** afforded the adducts **160** and **158b** in comparable amounts, which represent two alternative modes of reaction. Compound **158b** (X = OOH) is probably formed by an ene addition with atmospheric oxygen to the initially formed adduct. The vinylfuran **159** gave essentially a single product, the Diels–Alder adduct **161**, which was extremely unstable and spontaneously isomerized to **162** on standing at room temperature. Vinylfuran **1d** afforded cleanly the endo and exo adducts **163** and **164** in an approximate ratio of 2:1. No adducts derived from the reaction of the conjugated diene system containing the exocyclic double bond were obtained. Thus, the exocyclic double bond in **158** was highly reactive, in contrast to that of **1d**. These differences may be attributed to the inductive and resonance effects of the substituents.



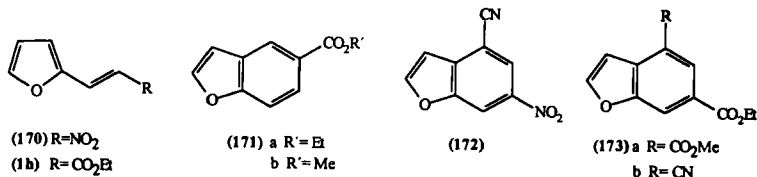
Olefins **165a–h** react with vinylfuran **112**, giving cycloadducts characterized as 5,6-dihydrozeno[*b*]furan-7(4*H*)-ones **166**, which are oxidation products of the nonaromatized primary cycloadducts **167** [84JCR(S)218]. The cycloadditions with unsymmetrical dienophiles, diethyl fumarate, and maleate proceeded with regio- and stereoselectivity. The products always had an electron-withdrawing group at the 4-position. When the dienophile was triethyl ethylenetricarboxylate **165i**, compound **112** reacted in a differ-

ent way and the open-chain adduct **168** was obtained, presumably via a zwitterionic intermediate **169** by silyl group migration to the anionic center (Z) (83H1933). Compound **112** also reacted with TCNE to give the cycloadduct **166j** when heated under an inert atmosphere [84JCR(S)218].



2-( $\beta$ -Nitrovinyl)furan **170** gave Diels–Alder cycloaddition with ethyl acrylate and methyl acrylate to furnish directly 5-carbomethoxy- and 5-carbomethoxybenzofurans **171a,b**, respectively (90SC101). Direct formation of aromatic product involved loss of  $HNO_2$ . The reaction with acrylonitrile resulted in the formation of disubstituted benzofuran **172** through dehydrogenation. In this case nitrite was not eliminated during aromatization and the regioselectivity is opposite.

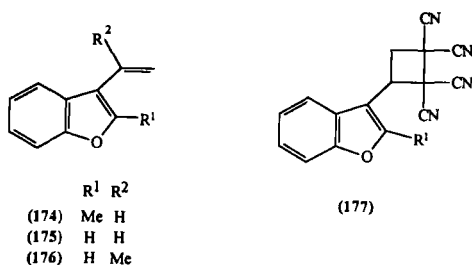
Tetrahydrobenzofurans **173a,b** were obtained from the Diels–Alder reaction of 2-( $\beta$ -carbomethoxyvinyl)furan **1h** with methyl acrylate and acrylonitrile.



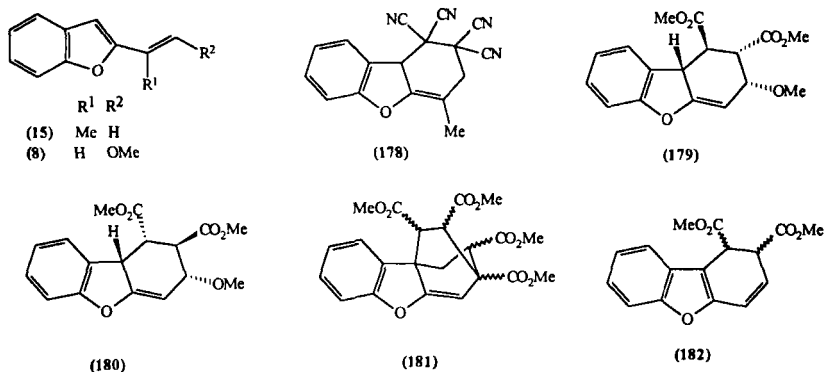
## 2. Vinylbenzofurans

Vinylbenzofurans also react as dienes in Diels–Alder reactions with acyclic olefins. The 3-vinylbenzofurans **174**, **175**, and **176** gave the normal adducts resulting from  $(4\pi + 2\pi)$ -cycloaddition in its reaction with TCNE. A by-product from the reaction of the diene **174** and TCNE was the cyclobutane **177** (91AJC1085).

2-Isopropenylbenzofuran **15** gave the same type of nonaromatic cycloadduct when it reacted with TCNE. Compound **178** had no tendency to



rearrange because of the low degree of aromaticity of the benzofuran ring system (70AJC2119). *trans*-2-( $\beta$ -Methoxyvinyl)benzofuran **8** reacted with dimethyl fumarate to give a mixture of three adducts—the two diastereoisomeric monoadducts **179** and **180**, corresponding to the two modes of addition of dimethyl fumarate, and the bis adduct **181**. This compound must arise by initial 1,4-elimination of methanol from **179**, **180**, or both, to give an intermediate 1,2-dihydrodibenzofuran **182**, which subsequently reacts with excess dimethyl fumarate to give **181**, presumably a mixture of stereoisomers.

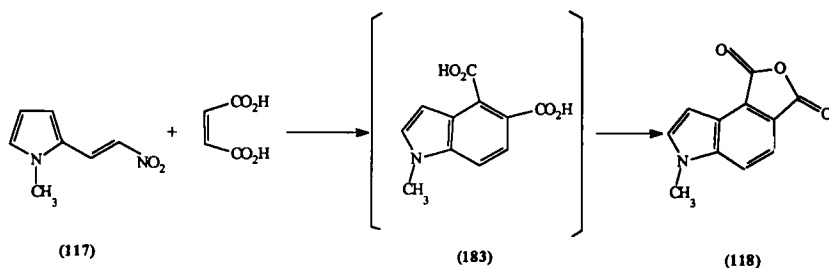


### 3. Vinylpyrroles

1-Substituted 2- and 3-vinylpyrroles react easily with electron-deficient dienophiles to provide dihydro- and tetrahydroindoles in a two-step process, the second step involving a (1,3)-sigmatropic hydrogen migration leading to aromatization of the five-membered ring (80JOC4515). There are examples of reactions with dimethyl maleate, *cis*- and *trans*-1,2-dicyanoethenes, acrylonitrile, and ethyl acrylate. The cycloadditions are concerted and the regioselectivity with the monosubstituted alkenes to give exclusively the 4-substituted tetrahydroindoles are consistent with

FMO calculations for the HOMO(vinylpyrrole)/LUMO(alkene) interactions.

The nitrovinyl system has been found to be a better diene than the corresponding vinyl analogs. Condensation of 1-methyl-2-(2-nitrovinyl)pyrrole **117** with maleic acid yielded *N*-methylindole-4,5-dicarboxylic anhydride **118**. Failure to isolate the expected diacid **183** is probably due to cyclization to the anhydride in the acidic medium created by the elimination of nitrous acid during the condensation. This process is believed to follow the normal Diels–Alder [4+2]-cycloaddition pathway with subsequent loss of nitrous acid [73JCS(P1)2450].

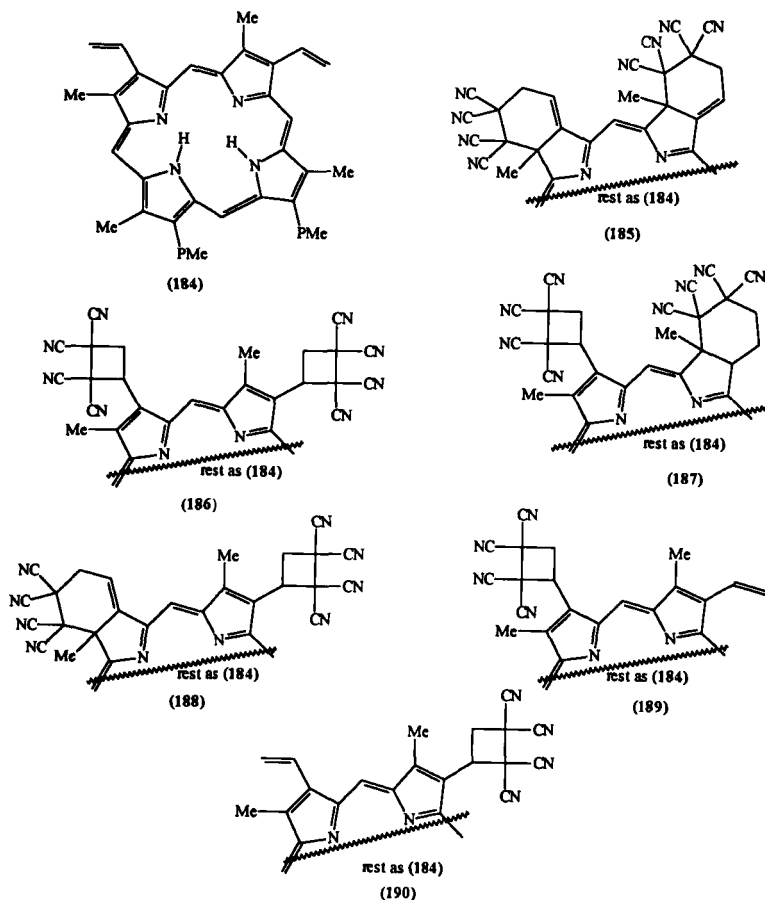


The reaction with dienophiles of the sulfur-substituted 3-vinylpyrrole, generated *in situ* by the alkylation of the 3-thioacetylpyrrole, has also been utilized to obtain indoles. Reactions with dimethyl maleate, dimethyl fumarate, methyl acrylate, acrylonitrile, and acrolein gave the corresponding cycloadducts which were directly transformed to the corresponding indoles by treatment with DDQ (91CPB489).

No reaction has been found with simple vinylpyrroles and TCNE. Nevertheless, there are examples of Diels–Alder reaction of some protoporphyrins with this dienophile. It was first reported [73JCS(P1)1424] that compound **184** reacted with TCNE in refluxing chloroform, giving the cycloadduct **185** in 56% yield. A later study reexamined the reaction and found more complicated chemistry (80JOC5196). In initial experiments, reactions of TCNE with protoporphyrin di-*tert*-butyl ester were shown to give three major products, **186**, **187**, and **188**; but depending on the conditions of the reaction, time, solvent or amount of TCNE, the results were different. The authors also characterized compounds **189** and **190**.

The reaction of TCNE with vinyl-bearing porphyrins is therefore a situation in which an apparent competition exists between a concerted Diels–Alder [4+2]-cycloaddition and a stepwise [2+2]-reaction proceeding through a dipolar intermediate. In this case the [2+2]-adduct was apparently the kinetically favored product while the [4+2]-adduct was favored thermodynamically.





Compound **184** also reacted with  $\beta$ -phenylsulfonylacrylonitrile to give the corresponding Diels–Alder adduct (84CC1047).

#### 4. Vinylindoles

There have been no reports of the formation of TCNE adducts from the parent 3-vinylindole. The electron-deficient dimethyl indol-3-ylfumarate **191** gave with TCNE adduct **192** in high yield (62DIS3851). Similar reactions with 1-*p*-toluenesulfonyl-3-vinylindole **193** and 1-acetyl-3-vinylindole **194** gave compounds **195** and **196** (77AJC1531; 88H2353; 92JOC910).

The behavior of the *N*-methyl dienes toward TCNE was quite different; they were all more reactive. The adducts from 3-isopropenyl-

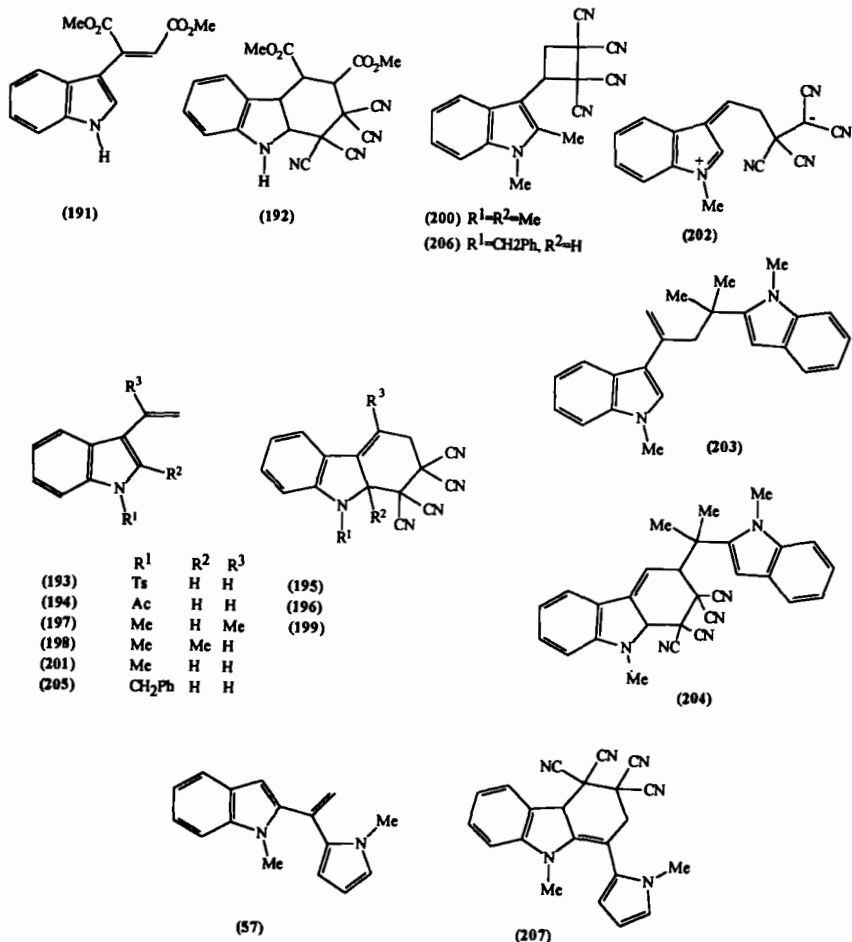
1-methylindole **197** and 1,2-dimethyl-3-vinylindole **198** were the tetrahydrocarbazole **199** and cyclobutylindole **200** structures, respectively. Evidence for the structure of the adduct from 1-methyl-3-vinylindole **201** and TCNE is less clear-cut. A study of the spectroscopic data of the adduct showed that there is an equilibrium between structures of [4 + 2]- and [2 + 2]-adducts. The former is apparently favored in benzene at 20°, and the latter in liquid sulfur dioxide at -35°. The resonance-stabilized zwitterion **202** is a likely intermediate in the conversion of these compounds, and its formation is not surprising since liquid sulfur dioxide is known to promote ionization of covalent compounds because of its high anion-solvating power [69JCS(B)77]. Attempts to trap the zwitterion **202** have been made, but were unsuccessful, so the initial Diels-Alder reaction must be classified as concerted. The 3-isopropenyl-1-methylindole gave dimer **203** when passed through an alumina column; this compound is also an efficient diene in the Diels-Alder reaction, and with TCNE gives the adduct **204** in high yield.

In the case of vinyl compound **205** in the reaction with TCNE, the ultraviolet spectrum of the adduct was that of a simple indole rather than that of the *o*-aminostyryl chromophore of the [4 + 2]-adduct, suggesting that the adduct is the cyclobutane **206** from a [2 + 2]-cycloaddition (81AJC1483).

Clearly, there is a fine balance between [2 + 2]- and [4 + 2]-cycloaddition in the reaction of TCNE with vinylindoles. The cycloaddition of 1-methyl-3-vinyl compound and TCNE in benzene gives mainly the [4 + 2]-product, although a small amount of the [2 + 2]-adduct also appeared to be formed. In liquid sulfur dioxide this [4 + 2]-adduct completely isomerized to the [2 + 2]-product. It is probable that in the reaction between diene **205** and TCNE the transition state for [4 + 2]-cycloaddition is destabilized by the steric requirements of the bulky *N*-benzyl group.

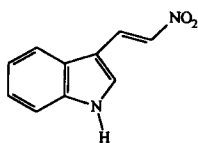
2-Vinylindoles also reacted with TCNE. Thus, compound **57** gave the carbazole derivative **207** (89JHC1869). In this case no competition between [4 + 2]- and [2 + 2]-cycloaddition was observed.

Both 3- and 2-vinylindoles react with other olefins to give Diels-Alder cycloadditions. The 3-vinylindoles **129**, **208**, and **209** reacted with acrylonitrile, ethyl acrylate, and cinnamaldehyde, giving the corresponding Diels-Alder adducts following aromatization by loss of a nitro group when it was present in the diene [86IJC(B)1038]. In the reactions with compound **209a**, it was possible to trap the tetrahydro intermediate **210** when the reaction mixture was heated at 120–125°C. Compound **209b** reacted with methyl acrylate in a similar way and the (*E/Z*) mixture of **209c** reacted with the same dienophile under Lewis catalysis to afford the endo cycloadduct **210c** and the exo cycloadduct **210d**, respectively (87HCA1419).

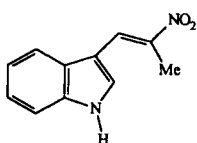


The *S*-benzyl derivative of 3-vinylindole **211** reacted with methyl maleate and fumarate (89CPB1999) in a sealed glass tube at 100°C under a nitrogen atmosphere, giving the unstable **212**, the structure of which was identified by transformation to **213** via reaction with active MnO<sub>2</sub>.

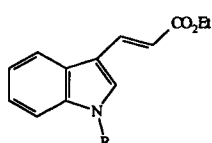
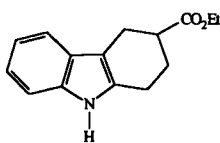
An interesting paper reports the combined synthesis of 3-vinylindoles from ketones with the vinylindole synthesis of tetrahydrocarbazoles in one flask by using indole (1 equivalent) and excess ketone precursor as the solvent, usually at reflux with maleic acid (1 equivalent), both as the catalyst for 3-vinylindole formation and as the dienophile for the Diels–Alder reaction. These reactions constitute an “*in situ* vinylindole synthesis of tetrahydrocarbazoles” (79JOC4402).



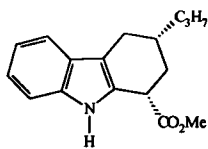
(219)



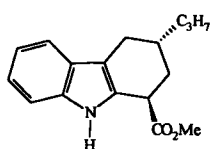
(208)

(209) a R = H, R<sup>1</sup> = CO<sub>2</sub>Etb R = Me, R<sup>1</sup> = CO<sub>2</sub>Etc R = SO<sub>2</sub>Ph, R<sup>1</sup> = C<sub>3</sub>H<sub>7</sub>

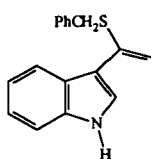
(210)



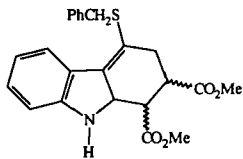
(210c)



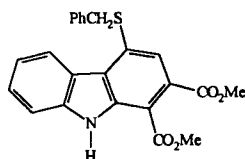
(210d)



(211)



(212)



(213)

Examples with 2-vinylindoles are also found. Thus, the reaction of *N*-methyl-2-(2-methoxyvinyl)indole, as a *cis-trans* mixture, with acrylonitrile and ethyl and methyl acrylate gives the corresponding Diels–Alder compounds [83IJC(B)846]. With *N*-methyl-2-(2-nitrovinyl)indole as diene, similar reactions occur with methyl acrylate, acrylonitrile, and acrolein acetal; but in these cases, the fully aromatic compounds were isolated. The cycloaddition reaction with acrolein acetal was nonregioselective and the isolated adducts had a CHO group, indicating that the acetal had been hydrolyzed (presumably during work-up).

The parent 2-vinylindole and 2-(2-methylvinyl)indole also reacted with the carbodienophiles methyl-(*E*)-3-benzoylacrylate, 1-penten-3-one, and methyl acrylate; these reactions proceeded through a Diels–Alder step to produce the corresponding carbazoles (90JOC5368). The unsymmetrical dienophiles reacted regioselectively in accordance with the predictions of the FMO concept. In none of these reactions was it possible to detect either a betaine intermediate originating from a stepwise process or a Michael-type adduct. The stereochemistry of the cycloadducts was not changed when the reactions were carried out in the polar solvent

methanol. Thus the authors consider that the first step of the sequence is a concerted HOMO(diene)/LUMO(dienophile)-controlled Diels–Alder process.

$\alpha,\beta$ -Unsaturated ketones and aldehydes react with acceptor-substituted 2-vinylindoles by trifluoroacetic acid (TFA) induction under very mild conditions (92TL6621). The cycloaddition products undergo a subsequent (1,3)-hydrogen shift, as is usual in the reactions of 2-vinylindoles, leading to regio- and stereospecific carbazole derivatives. Thus, the reaction of 2-ethylprop-2-enal with  $\alpha$ -ethylidene (*Z*)-1*H*-indole-2-acetonitrile and TFA in chloroform at room temperature afforded a tetrahydrocarbazole in 58% yield with the configuration at the C1, C2, and C3 atoms fully determined. In its reaction with cyclohexenone, another tetrahydrocarbazole was obtained in 40% yield, generating stereoselectively four adjacent asymmetric carbon atoms with *cis* configuration of their substituents. With 3-substituted-2-vinylindoles, a (1,3)-hydrogen shift is impossible and the endo primary cycloadducts were formed.

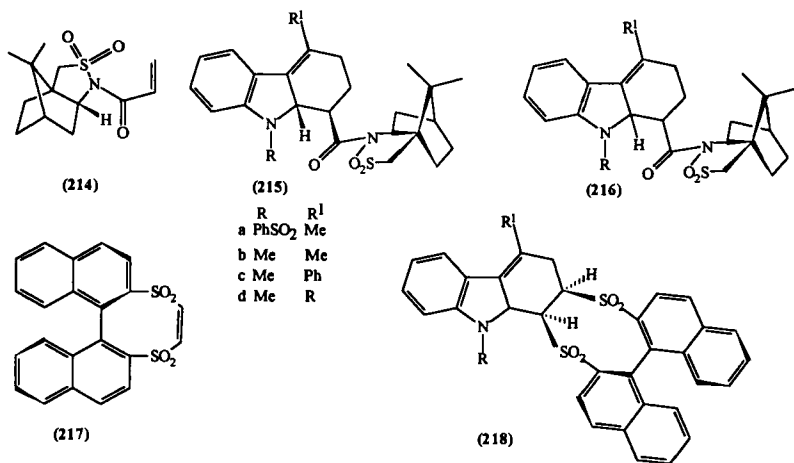
The dimerization of the 2-vinylindoles could be observed as a side reaction when high concentrations of 2-vinylindoles were used. The formation of this by-product could be avoided by using montmorillonite as an acidic ion exchanger (71JOC1759).

The reactivity of the ethyl-2-(1-methyl-2-indolyl)acrylate, as diene, toward the dihydropyridine, as dienophile, was investigated to determine the cycloaddition reaction conditions (74MI1) that could, ultimately, lead to Aspidosperma- and/or Iboga-type alkaloids via a biomimetic pathway resembling the proposed intramolecular Diels–Alder cyclization of the hypothetical intermediate dehydrosecodine into tabersonine and catharanthine (80JOC1657; 81CC37). The dihydropyridine reacted both as a diene and dienophile with respect to the acrylate, giving the Iboga and Aspidosperma analogs.

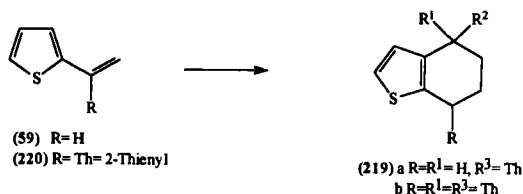
The reaction of 2- and 3-vinylindoles with dienophile **214** constitutes the first example of an asymmetric Diels–Alder reaction of vinyl heterocycles. From 3-vinylindoles, enantiomerically pure carbazoles **215a–c** were obtained, whereas from the vinylindole **197** together with **215d**, diastereomer **216** was obtained as a minor product. Conversely, 2-vinylindoles provided inseparable mixtures of diastereomeric carbazoles. On the other hand, the cycloaddition reactions of 3-vinylindoles with **217** furnish the tetrahydrocarbazoles **218** with endo-diastereoselectivity (93T2863).

## 5. Vinylthiophenes

2-Vinylthiophene **59** underwent thermal dimerization, as did 2-vinylfuran (Section II,D,1), to give compound **219a** (69MI1). In a similar way, the



vinyl compound **220** also dimerized thermally, giving the corresponding [4 + 2]-adduct **219b** (91CB1203).



It is also known that 2- and 3-vinylthiophene react with methyl acrylate, giving the expected Diels–Alder adducts with the thiophene ring rearomatized (85T2435; 87T269). In both cases the cycloaddition was regioselective in the sense predicted by simple Hückel MO calculations.

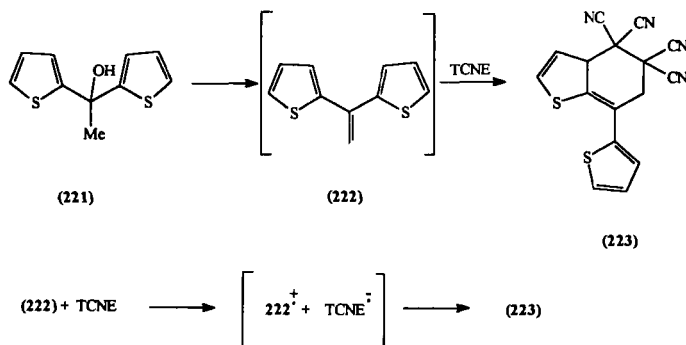
With  $\alpha$ -trimethylsilyloxyvinylthiophene **144** the reactions with the olefins **165a–j** work in a way similar to that with vinylfurans (Section II,D,1) [84JCR(S)218]. Only in the case of the olefin (*E*)-1,2-dicyano-1,2-bis(ethoxycarbonyl)ethylene **165i** was the corresponding primary adduct isolated.

The reaction of 1,1-bis(2-thienyl)ethanol **221** with TCNE at room temperature afforded a white crystalline compound identified as cycloadduct **223** in quantitative yield (90H1873). The formation of **223** is easily understood as a [4 + 2]-cycloaddition of 1,1-bis(2-thienyl)ethylene **222**, formed by dehydration of alcohol **221** and TCNE. The reaction was unusually fast, it took place in less than 15 minutes and did not need any source of heat or light to be promoted. Since other vinylthiophenes participate in Diels–Alder reactions to give aromatic cycloadducts under rather severe conditions (Section II,A,5), the authors suggested that the reaction

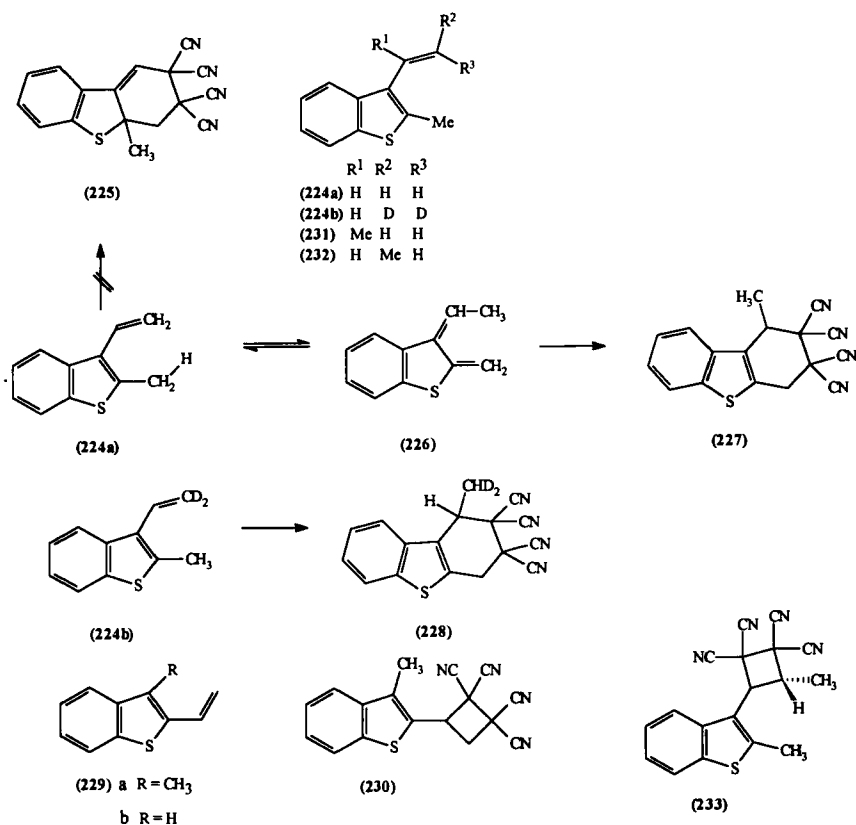
occurred by electron transfer through radical-ion pairs as shown in Scheme 8.

## 6. Vinylbenzothiophenes

3-Vinylbenzo[*b*]thiophenes have received more attention than vinylthiophenes. The parent diene 3-vinylbenzothiophene and different  $\alpha$ - and  $\beta$ -substituted vinylbenzothiophenes afforded the same type of [4+2]-cycloadducts (72TL255; 79AJC133). Diene **224a**, like those discussed above, gave a 1:1 adduct, but the spectroscopic data were not compatible with the expected structure **225**. However, these data completely agree if the adduct has the isomeric structure **227** (72TL4728). The formation of **227** is most readily explained as the result of a symmetry-allowed (65JA2511) thermal 1,5-hydrogen transfer to give the rearranged diene **226**, which then gives the adduct **227** by a normal [4+2]-cycloaddition. That this mechanism describes most of the features of the rearrangement was shown by the isolation of the dideuteromethyl adduct **228** when the dideuterovinylbenzo[*b*]thiophene **224b** was allowed to react with TCNE. The simple six-center mechanism for the rearrangement suggests that the postulated diene isomerization should be reasonably common if the basic structural requirements (a methyl group and a vinyl group in a 1,2-relationship on an aromatic ring) are met. The 3-methyl-2-vinylbenzothiophene **229** and TCNE gave the normal adduct together with the cyclobutane **230**, while **231** gave only the normal adduct and **232** gave the cyclobutane **233** (79AJC133). The reaction of 2-vinylbenzo[*b*]thiophene with TCNE gave, interestingly, the normal adduct in good yield [89IJC(B)724].

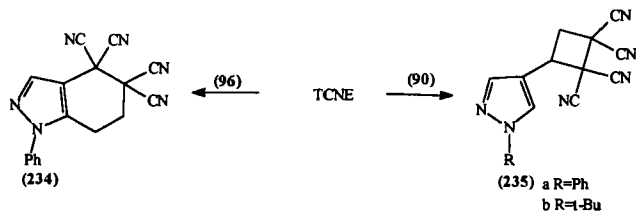


SCHEME 8



## 7. Vinylpyrazoles

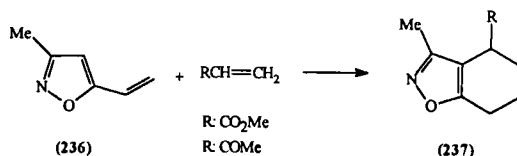
There are a few examples of the participation of the pyrazole ring in Diels–Alder cycloadditions with acyclic olefins. In the reaction of 1-phenyl-5-vinylpyrazole **96** and TCNE, the tetrahydroindazole **234** was obtained. 1-Phenyl- and 1-*tert*-butyl-4-vinylpyrazoles **90a** and **90c** react similarly with different dienophiles, but TCNE reacted in a different way and the [2 + 2]-cycloadducts **235** were isolated (86T6683; 89M1113).





## 8. Vinylisoxazoles

The use of isoxazole derivatives in organic synthesis is of great interest, but little has been done on the utilization of such compounds as a part of a diene system in [4 + 2]-cycloadditions. 3-Methyl-5-vinylisoxazole **236** gave cycloaddition reactions in a sealed tube in benzene solution at 120°C for 3 days. With the dienophiles acrolein and methyl acrylate, aromatization of the isoxazole ring via a 1,3-proton shift occurs readily under the reaction conditions, allowing the direct isolation of compounds **237**, which are also detected in the mass spectrum of the raw reaction material. The reactions are regioselective (85H2019).

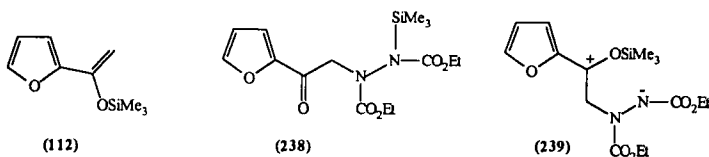


## III. Reactions of Vinyl Heterocycles with Heterodienophiles

### A. REACTIONS WITH AZODIENOPHILES

#### 1. Vinylfurans

No examples were found in the literature of the reaction of the parent vinylfuran with azo compounds. Only the 2-(1-trimethylsilyloxy) derivative **112** is reported to react with diethyl azodicarboxylate (DEAZD) to give the open-chain adduct **238**, presumably via a zwitterionic intermediate **239**, followed by a silyl-group migration to the anionic center [83H1933; 84JCR(S)218].



#### 2. Vinylbenzofurans

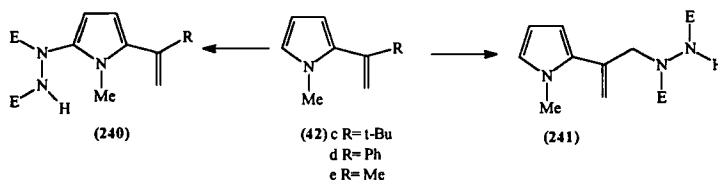
The 3-vinylbenzofurans **174** and **175** reacted in the normal fashion with the highly reactive dienophile 4-phenyl-1,2,4-triazole-3,5-dione (PTAD)

to give the corresponding benzofuro[2,3-*c*]pyridazine derivatives. There is no evidence for reactions occurring with rearrangements or cyclobutane formation (91AJC1085).

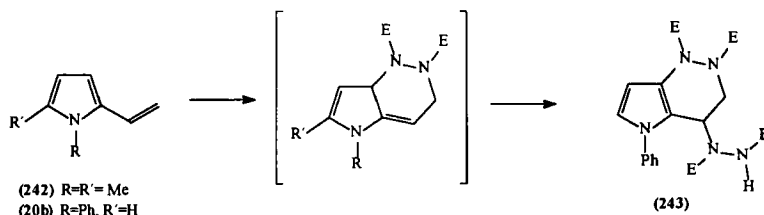
### 3. Vinylpyrroles

The reactivity of 2-vinylpyrroles with DEAZD is strongly dependent upon steric factors. When the vinylpyrroles presented some steric inhibition to the coplanarity of the diene system by substituents on the vinyl group, as in compounds **42c** and **42d**, reaction with DEAZD gave Michael adducts **240** at the 5-position of the pyrrole ring. This behavior was similar to the reaction of other simple pyrroles, indolizines (80JOC1692, 80TL3673) and isoindoles (90TL3471) with DEAZD and also analogous to the low-temperature reaction of 2-vinylpyrroles **5b** with DMAD.

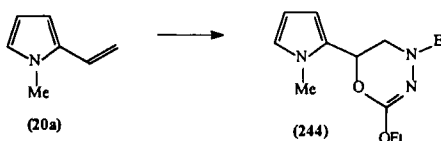
In contrast, 2-(1-methylpyrrol-2-yl)propene **42e** afforded an ene adduct **241** [85JCR(S)12].



When the 5-position of the pyrrole ring is substituted, as in 1,5-dimethyl-2-vinylpyrrole **242**, or when there is a substituent on the *N*-ring (Ph) as in compound **20b**, the Michael type reaction is sterically inhibited at the 5-position. A 1:2 adduct, **243**, was formed as a result of an initial [4+2]-cycloaddition followed by a further ene reaction with a second molecule of DEAZD [85JCR(S)12].



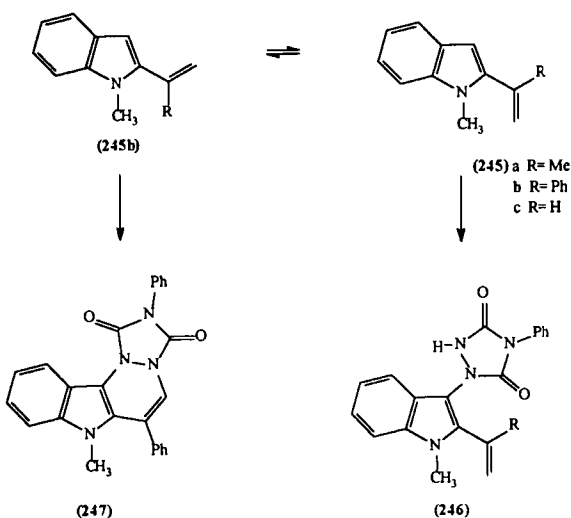
The reaction of 1-methyl-2-vinylpyrrole **20a** with DEAZD was less defined, and a major component in a complex mixture of photoreactive and thermally labile products was isolated. Spectral data indicated it was the oxadiazine **244** [85JCR(S)12].



#### 4. Vinylindoles

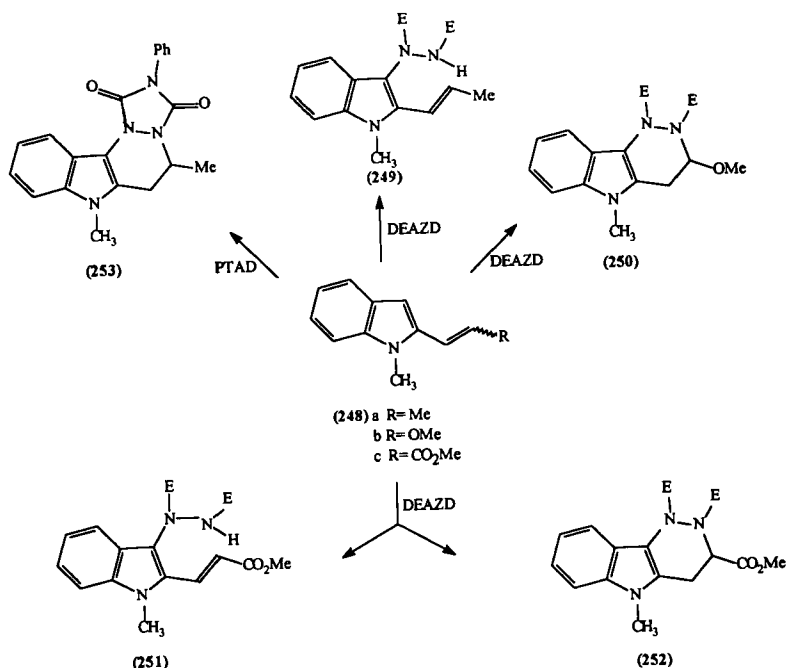
In contrast with 2-vinylpyrroles, the reactions of 1-methyl-2- and -3-vinylindoles with DEAZD were extremely complex, and many unstable products were detected in low yield (86TH1).

With the more reactive dienophile PTAD, 1'-substituted 1-methyl-2-vinylindoles **245a** reacted readily at 20°C to produce the stable crystalline 1-(1-methyl-2-vinylindol-3-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione **246** in high yield (87H401). However, using other reaction conditions (CH<sub>2</sub>Cl<sub>2</sub>, 40°C, 3 days), 1'-phenyl-2-vinylindole **245b** afforded the Diels–Alder cycloadduct **247** (12%), and the Michael adduct was detected in trace amounts only by thin-layer chromatography (TLC) (88H967). In the reaction of 1-methyl-2-vinylindole **245c** with PTAD only a polymeric material was obtained [85JCR(S)12], probably due to its instability and susceptibility to dimerization even at relative low temperatures (71JOC1759).



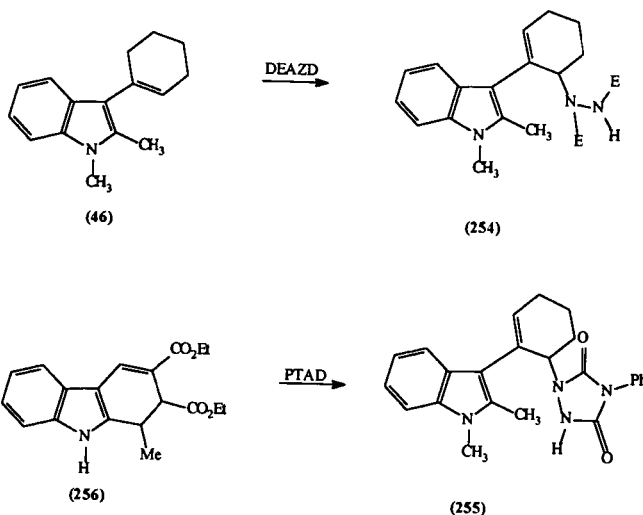
2-Vinylindoles bearing donor or acceptor substituents on the vinyl group, **248a-c**, reacted with DEAZD, affording Diels–Alder or Michael adducts (88H967). For example, the (*E*)-isomer **248a** reacted with DEAZD to furnish the Michael adduct **249**. The electron-rich (*E/Z*)-methyl enol

ether **248b** gave exclusively the Diels–Alder cycloadduct **250**, and the (*E*)-methyl indole-2-acrylate **248c** afforded a mixture of Michael adduct **251** and Diels–Alder adduct **252**. In the reaction of the 2'-substituted 2-vinylindoles with the highly reactive PTAD, only **248a** gave a defined product (**253**; 32% yield). (*Z*)-2'-Methoxy-1-benzenesulfonyl-3-vinylindole reacted stereospecifically with PTAD and DEAZD to furnish Diels–Alder cycloadducts. The reaction with the (*E*)-isomer gave rise to unstable and uncharacterizable products (92JOC910).

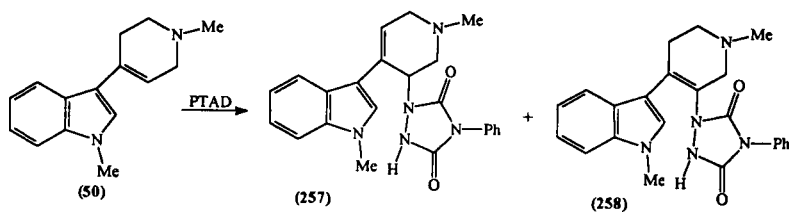


The vinyl function can be incorporated into a carbocyclic ring. In this context the reactivity of the readily available 3-(1-cyclohexenyl)indole **46** toward different dienophiles was studied (91LA357). In some cases (DMAD, NPMI) the Diels–Alder cycloadducts were obtained (Sections II,A,4 and II,C,4); however, reaction with DEAZD and PTAD afforded the ene adducts **254** and **255**.

Although dihydrocarbazole **256** has a fixed 1-aminobutadiene unit and should be able to participate in Diels–Alder reactions as a diene component, no cycloadditions took place with a series of hetero- and carbodienophiles. In the reaction with PTAD, 1,2-dihydrocarbazole **256** was dehydrogenated to the corresponding carbazole (91LA357).



The synthesis of the vinylindole **50** with the vinyl function incorporated into a tetrahydropyridine ring was made with the purpose of establishing new strategies for the synthesis of pyrido[*c*]-annelated carbazoles, analogs of the highly antitumoric ellipticine (91TL1771). Reactions as a dienes succeed only with DMAD and NPMI (Sections II,A,4 and II,C,4). However, with PTAD this compound was transformed to an inseparable mixture (3 : 2) of the ene adduct **257** and the Michael adduct **258**. With this vinylindole the DEAZD behaved as an oxidizing agent and gave rise to the dehydrogenated pyridinium salt and the hydrazine (91HCA430, 91TL1771).

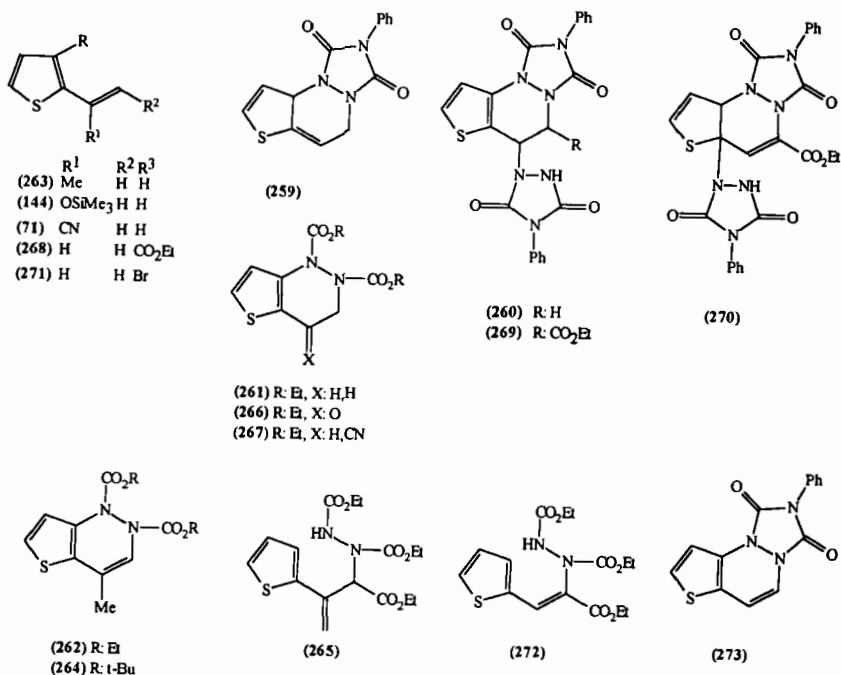


1,1-Bis(3-indolyl)ethenes **127** also react as a 4 $\pi$ -electron system and with PTAD the corresponding Diels–Alder adduct was isolated in 43% yield (86C124).

### 5. Vinylthiophenes

The first report of reactions of vinylthiophene with azodienophiles appeared in 1974: The reaction between 4-phenyl-1,2,4-triazolin-3,5-dione

(PTAD) and 2-vinylthiophene **59** in methylene chloride at  $-20^\circ$  gave a Diels–Alder adduct for which the structure **259** was proposed (74JA5591). Evidence for this structure was slight, and no physical or spectral data were given. Later, it was reported that the NMR data clearly ruled out a structure with an aromatic thiophene ring [84JCS(P1)915]. When the same reaction was carried out in ether as solvent at room temperature, one 2 : 1 adduct **260** was formed, presumably from the initial Diels–Alder adduct by ene reaction involving the allylic hydrogen at 9a-H with a second mole of PTAD.



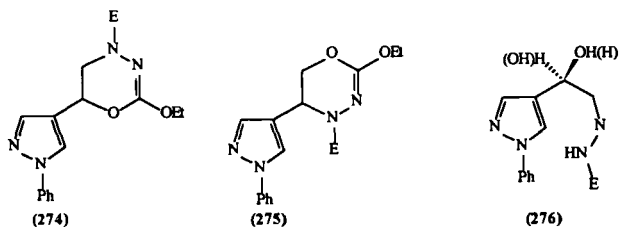
Diels–Alder cycloadditions of 2-vinylthiophenes with azodicarbonyl dienophiles were also investigated as an approach to the thieno[3,2-*c*]pyridazine system (79T2027). 2-Vinylthiophene reacted with diethyl or di-*tert*-butyl azodicarboxylate, giving mixtures of products that could not be separated by chromatography, but whose mass spectrogram showed molecular ions corresponding to tetrahydro- **261** and dihydrothieno[3,2-*c*]pyridazine **262**, both compounds having an aromatic thiophene ring. A sample of the mixture from the di-*tert*-butyl ester was treated with TFA and then oxidized, giving, after chromatography, a small yield of thieno[3,2-*c*]pyridazine.

Reactions of substituted vinylthiophene such as 2-(prop-1-en-2-yl)thiophene **263** are described with di-*tert*-butyl ester, giving two products—the dihydrothieno[3,2-*c*]pyridazine **264** (10%) and the ene addition product **265** (23.5%) (79T2027). When the substituent was a trimethylsilyloxy group (compound **144**), the reaction with DEAZD gave a [4 + 2]-cycloadduct **266** [83H1933; 84JCR(S)218]. The same reactant, DEAZD, with cyanovinylthiophene **71** also gave the “normal” adduct **267** in 55% yield (87T991).

Addition of PTAD to a solution of acrylate **268** at room temperature gave two products [84JCS(P1)915]; both were 2 : 1 adducts and they were assigned structures **269** (46%) and **270** (8%). Ene reactions with the initial Diels–Alder adduct involving the allylic hydrogens at the 9a and 5 positions would produce the 2 : 1 adducts **269** and **270**, respectively. These two adducts easily lost PTADH<sub>2</sub>, giving a dihydrothieno[3,2-*c*]pyridazine. All attempts to cleave the triazole ring were unsuccessful. Another attempt to form thieno[3,2-*c*]pyridazines was done with compound **260**, which did not eliminate PTADH<sub>2</sub>. The required compound **271** could be prepared by an alternative route: Reaction of PTAD with 3-bromo-2-vinylthiophene at room temperature in dioxane, followed by treatment with potassium carbonate to give the tricyclic compound **272** (46%) [84JCS(P1)915]. In view of these difficulties, the use of an alternative azodienophile was investigated. Diethyl azodicarboxylate did not react with acrylate **268** even on heating at 156°. However, using the Lewis acid boron trifluoride/ether as solvent, a low yield of a 1 : 1 adduct (15%) was obtained at room temperature. This product was not the required Diels–Alder adduct; it was identified as compound **273**.

## 6. Vinylpyrazoles

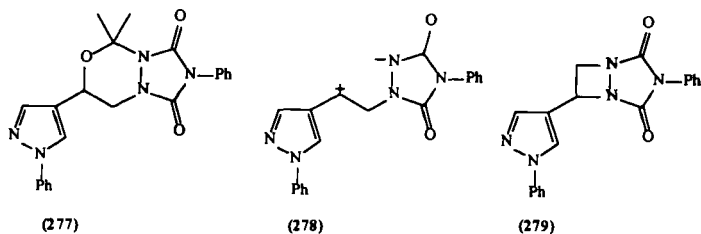
Although 1-phenyl-4-vinylpyrazole **90a** was recovered unchanged from reactions with acetylenic esters when mild conditions were used and cycloadducts were obtained only under pressure and high temperatures (Section II,A,7), the reaction with DEAZD proceeded smoothly in acetonitrile at about 80°C to yield a product characterized as a dihydrooxadiazine. However, the available spectral evidence did not distinguish unequivocally between the isomeric [4 + 2]-cycloadducts **274** and **275**. Crystallization of **274** from wet solvents resulted in its conversion into **276**. The same compound was obtained when the acetonitrile used in the reaction of **90a** with DEAZD had a small amount of water. X-Ray crystallographic analysis showed the compound to have structure **276**, thereby establishing **274** as the structure of the oxadiazine [84-JCS(P1)1423]. 1-*tert*-Butyl-4-vinylpyrazole **90c** also afforded a dihydrooxidiazine in the reaction with DEAZD (89M1113).



Since the reactions involve only the olefinic substituent, with no participation in the cycloaddition reaction of the pyrazole ring, the authors considered important the preparation of 1-phenyl-5-vinylpyrazole **96** and the study of its reactivity. Differences in electron densities and steric hindrance for the 4- and 5-positions of the 1-phenylpyrazole made it difficult to predict possible similarities in reactivity between 1-phenyl-5-vinylpyrazole **96** and 1-phenyl-4-vinylpyrazole **90a**; and the study showed that the reactivity of 1-phenyl-5-vinylpyrazole was lower, with reaction times longer than those required for the vinylpyrazole **90a**. With all the dienophiles used, included DEAZD, Diels–Alder adducts were obtained exclusively [90JCS(P1)2749].

As 1,2,4-triazole-3,5-dione (PTAD) is a stronger dienophile than acetylenic esters, more facile formation of the Diels–Alder cycloadducts was expected. But because it cannot behave as a diene in a reaction with alkynes such as diethyl azodicarboxylate, the formation of dihydrooxadiazines is excluded. In spite of these characteristics, no Diels–Alder adducts were obtained in the reaction of 1-phenyl-4-vinylpyrazole with PTAD in acetone at  $-80^{\circ}\text{C}$  and 2,2-dimethyl-4(1-phenylpyrazol-4-yl)-8-phenyl-1,6,8-triaza-3-oxabicyclo[4.3.0]nona-7,9-dione **277** was obtained as a major product. The isolation of the tetrahydrooxadiazine **277** indicates that the 1,4-dipole **278** was formed and trapped with acetone.

When the same reaction was carried out in dichloromethane, the unstable diazetidine **279** was obtained (85TL6357).

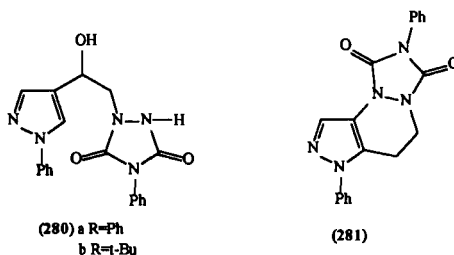


When dimethyl maleate was chosen to trap the 1,4-dipole generated in the reaction of PTAD with 1-phenyl-4-vinylpyrazole, the expected



[2 + 2]-adduct derived from the reaction of the 1,4-dipole with dimethyl maleate could not be detected, but partial isomerization of the maleate to dimethyl fumarate was detected. Moreover adduct **280a** (12%), generated by capture of the 1,4-dipole with water, precipitated from the crude reaction mixture [87JCR(S)384]. In the reaction of 1-*tert*-butyl-4-vinylpyrazole with PTAD, alcohol **280b** from capture of the 1,4-dipole with water was isolated in 81% yield. Spectral data were practically coincident with those of the adduct **276** obtained from the reaction of 1-phenyl-4-vinylpyrazole with DEAZD.

In contrast with the reactivity of 4-vinylpyrazoles with PTAD which involve just the olefinic double bond, 1-phenyl-5-vinylpyrazole reacted with PTAD as a diene, affording the Diels–Alder cycloadduct **281** [90JCS(P1)2749].

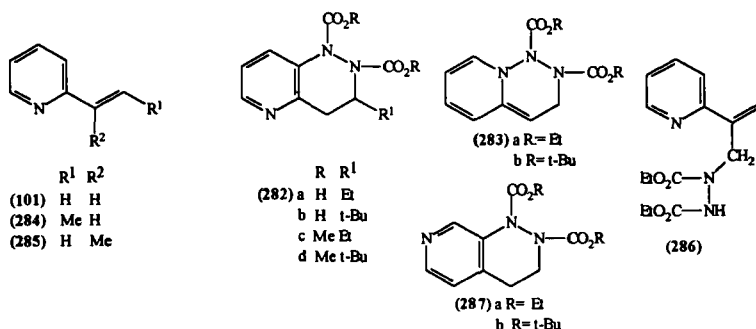


## 7. Vinylpyridines

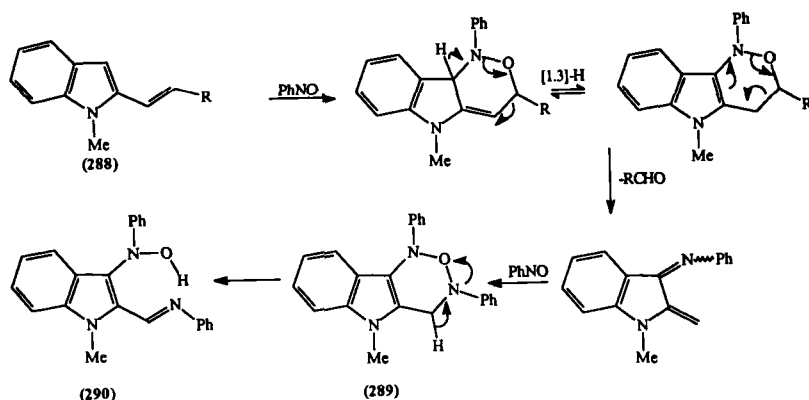
Reaction between 2-vinylpyridine **99** and diethyl- or di-*tert*-butylazodicarboxylates gave *N,N'*-disubstituted tetrahydropyrido[3,2-*c*]pyridazines **282a,b** and dihydro-3*H*-pyrido[1,2-*c*]triazines **283a,b**. 2-(Prop-1-en-1-yl)pyridine **284** gave hydropyridopyridazines **282c,d**, but 2-(prop-1-en-2-yl)pyridine **285** gave mainly the ene addition product **286**. From 4-vinylpyridine **156** and the same azo compounds, diesters of tetrahydropyrido[3,4-*c*]pyridazine-1,2-dicarboxylic acid, **287a,b** were obtained (78TL2731; 79T2027). The di-*tert*-butyl esters **282b,c** and **287b** are quantitatively decarboxylated in TFA, giving the corresponding tetrahydropyridopyridazines, which were oxidized to the fully aromatic compounds.

## B. REACTIONS WITH OTHER HETERODIENOPHILES

In contrast with azodienophiles, the heterodienophiles diethyl mesoxalate and chlorosulfonyl isocyanate reacted as electrophiles. Nitrosobenzene was an exception; in the reaction with vinylindole **288**, adduct **290**



was obtained as a result of a multistep sequence which included two regiospecific FMO-controlled Diels–Alder steps. The oxadiazine **289** cleaved during the process because of the lability of the N—O bond (89T6427).



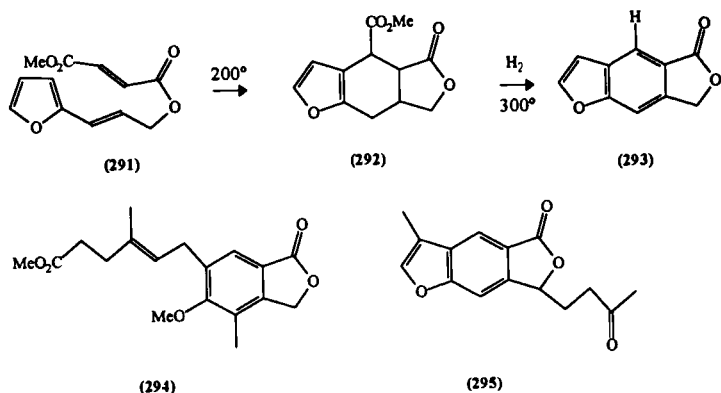
## IV. Intramolecular Diels–Alder Reactions

The intramolecular Diels–Alder reactions of vinyl heterocycles have been especially directed toward the syntheses of natural products.

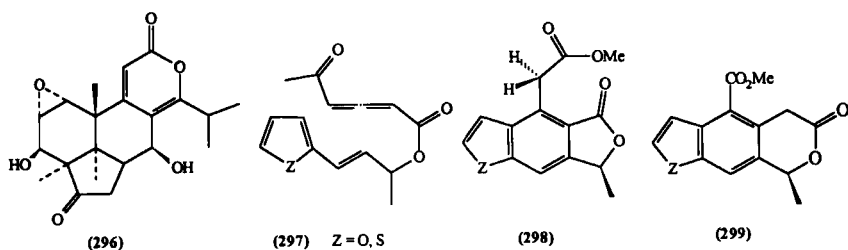
### A. FURANS

When heated in toluene at  $200^\circ\text{C}$ , the vinylfuran **291** afforded the adduct **292**. Dehydrogenation of **292** gave the benzofuran **293**, a key intermediate

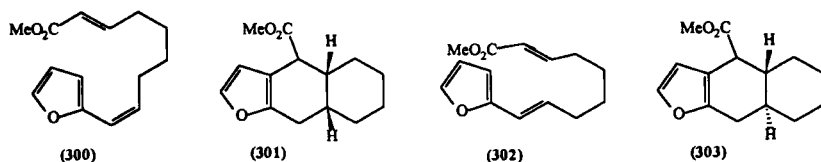
in the synthesis of the mycophenolic acid **294** and secofuranoteremophilane **295** (81CL917).



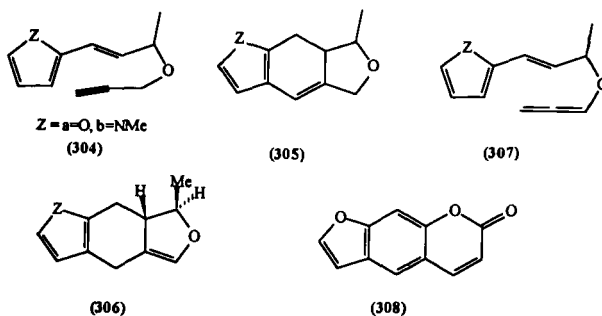
As a first approach to the synthesis of nagilactone **296**, a norditerpenoid isolated from Podocarpaceae, which inhibit the expansion and mitosis of plant cells, an intramolecular Diels–Alder reaction of allene 1,3-dicarboxylic acid esters was used. The cyclization of **297** afforded the  $\delta$ -lactone **298**, rather than the  $\gamma$ -lactone **299** [85JCS(P1)747].



Furanodecalins can be readily obtained in good yield using intramolecular cycloadditions of simple unsaturated esters as dienophiles. The (2*E*,8*Z*)-nonadienoate **300**, when heated to 290°C was converted into the *cis*-furanodecalin **301** in quantitative yield. Thermolysis of the (2*E*,8*E*)-nonadienoate **302**, gave *cis*-furanodecalin **301** and the *trans* isomer **303** in a ratio 45 : 55. The same methodology is equally suited to 3-vinyl furans (88TL2107).

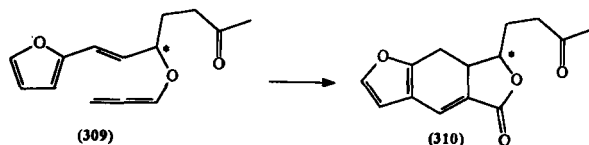


The propargyl ethers **304a,b** possessing a vinylfuran and a vinylpyrrole diene moiety afford the Diels–Alder adducts **305a,b** in 59% and 38% yields, respectively, when heated to 150°C in toluene in a sealed tube. The treatment of **304a,b** with *t*-ButOK in refluxing *t*-ButOH (83°C) resulted in the smooth formation of another type of Diels–Alder adduct **306a,b** in almost quantitative yields, probably via allene intermediates **307** (84JA6735).



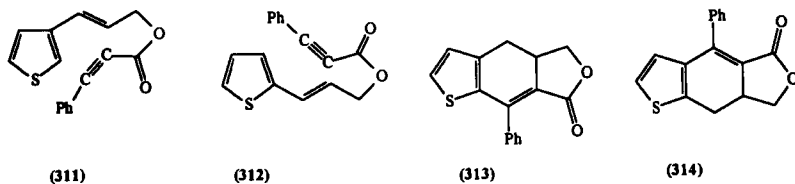
The facility of these reactions was attributed to the favorable geometry of the allenyl ether for intramolecular Diels–Alder reactions, compared with that of the propargyl ether. These methodologies were used in a new synthesis of a naturally occurring furocoumarin, psoralen **308**, which is of interest because of its unique photoreactions with DNA and its utility as a phototherapeutic agent.

Using a similar approach, the first asymmetric synthesis of the benzofuran lactone **310** was described, starting from the chiral ether **309** (88JOC860).



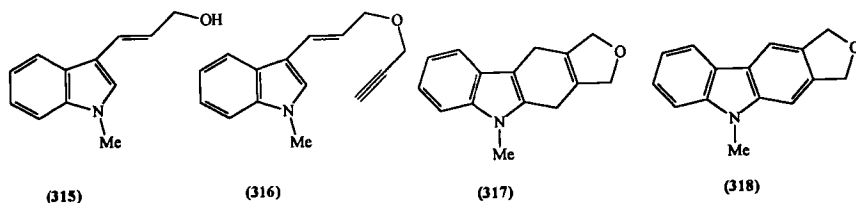
## B. THIOPHENES

Intramolecular reactions of 3-(2- and 3-thienyl)allyl phenylpropiolates **311** and **312** gave lactones **313** and **314**. Formation of **313** involves substitution into the 3-position of the thiophene, while formation of **314** involves substitution into its 2-position (65JHC225).

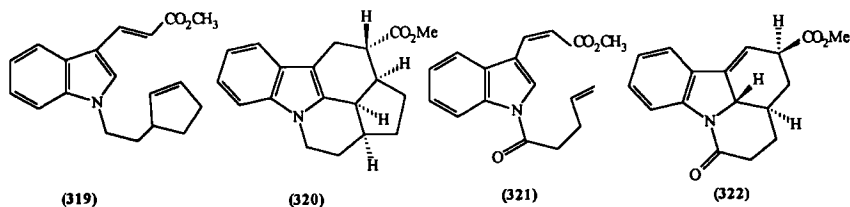


### C. INDOLES

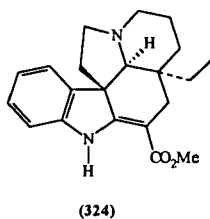
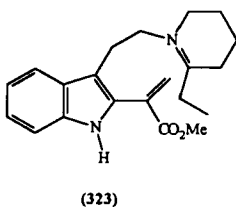
Starting from indolylallyl alcohol **315**, several compounds containing a diene–dienophile in their structures were prepared. The 3-vinylindole **316** underwent an intramolecular Diels–Alder reaction when heated in bromobenzene at 156°C, affording cycloadducts **317** and **318** (89CZ273).



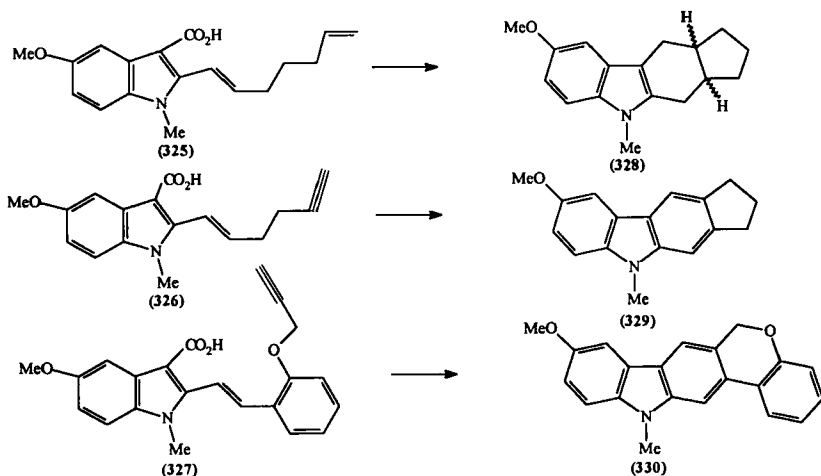
Other substrates suitable for intramolecular reactions were prepared by alkylation of indole-3-carboxaldehyde with 5-chloropentyne followed by a Wittig reaction. The indole-3-acrylate **319** was heated at 300°C and then dehydrogenated to the pyridocarbazole **320** (87JOC4661). A similar cyclization of the indole-3-acrylate **321** afforded the pentacyclic compound **322** (89H1871).



The corresponding intramolecular reactions of 2-vinylindoles have been less well studied as a result of difficulties surrounding their synthesis. Several examples are related to synthesis of *Aspidosperma* alkaloids and biomimetic studies, and include cycloaddition reactions of indole-3-acrylates **323** to afford pentacyclic compounds **324** (73JC7146; 78JOC3705; 79JOC2477; 80JOC1657; 81CC37; 85JOC924).



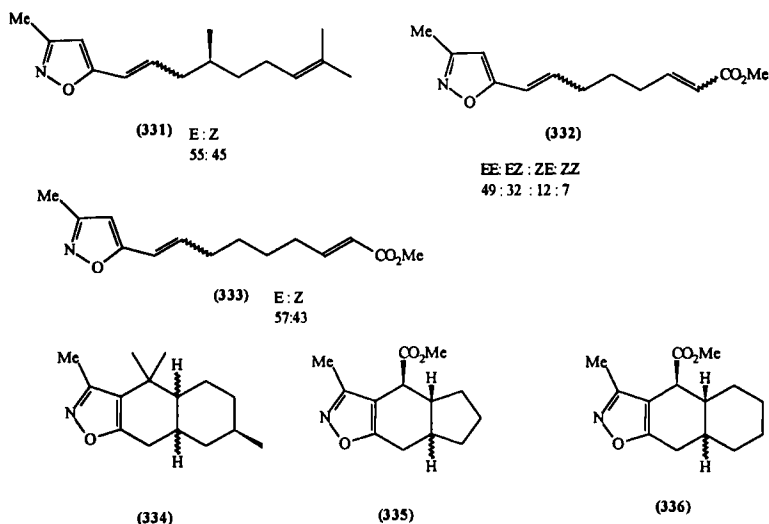
Indole-3-carboxylic acids **325**, **326**, and **327** afford the cycloadducts **328**, **329**, and **330** by intramolecular reactions. The conditions needed to effect cyclization were not especially mild (232°C, 8 hours for **2a**; 210°C, 7 hours for **2b**; refluxing nitrobenzene, 3 hours for **325**), and yields were better in the case of the alkynes **326** and **327**. The relative ease of reaction and greater yield for **326** and **327** were due to the smaller HOMO/LUMO energy gap between the relatively electron-rich 2-vinylindole diene and the relatively electron-poor alkyne (compared to an olefin) (90H993).



#### D. ISOXAZOLES

The participation of the isoxazole ring in cycloaddition reactions (Section II,D,8) prompted the same authors to test the possibility of achieving intramolecular cycloadditions (87H47). Intramolecular cycloaddition was successful with substrates **331**, **332**, and **333** in  $\text{CHCl}_3$  in a sealed tube above 150°C; the cycloadducts were observed by GC-MS monitoring. After 48 hours at 200°C, the isoxazole **331** showed only a 10% conversion to a mixture of cycloadducts **334**. The more activated substrates **332** and

**333**, however, after 36 hours gave the respective cycloadducts **335** and **336** as mixtures of their *cis* and *trans* stereoisomers (due to carbocyclic ring fusions) in 3 : 1 and 1 : 2 : 1 ratio, respectively. The aromatized product was the only one detected by GC–Ms.



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